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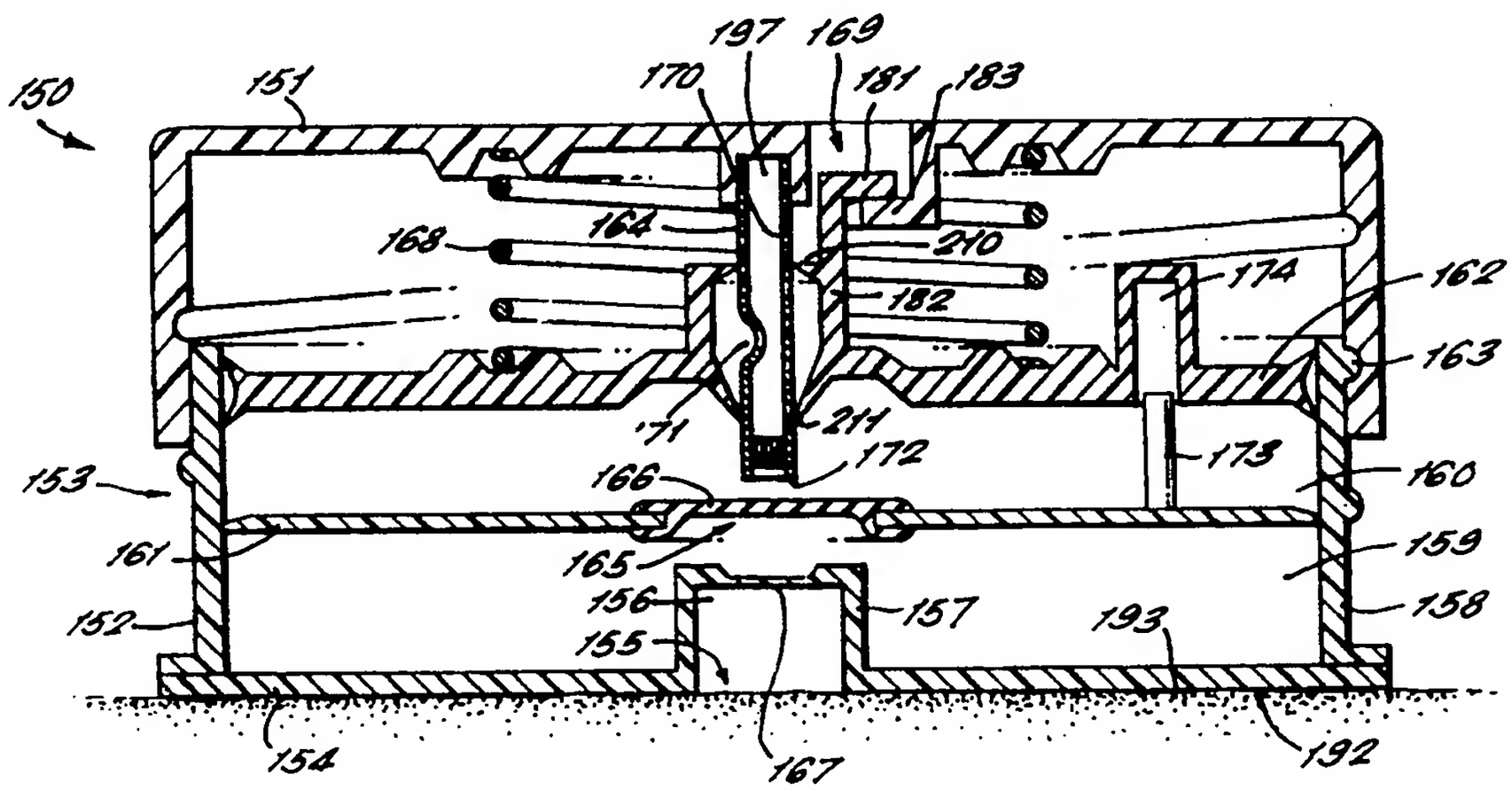

(57) Abstract

Apparatus (150) has a housing (153) attached to the skin adhesively and defines a chamber (156) within which suction is applied at a treatment site. After formation of a suction blister the blister is disrupted to expose a dermis layer of skin from which the epithelium has been removed. Liquid drug is then introduced into the chamber for transdermal perfusion directly through the dermis. Suction is applied to the chamber without connection to an external source of suction by means of an evacuated cell (158) separated from the chamber by a disruptable membrane (167). A tubular member (164) is actuated to rupture the membrane, disrupt the blister and deliver liquid to the chamber in successive stages of operation of the apparatus.

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"TRANSDERMAL PERFUSION OF FLUIDS"

This invention relates to transdermal perfusion of fluids through the skin of the human or animal body and in particular but not exclusively to apparatus for de-epithelialising the skin by the suction blister method to enable perfusion to take place directly via the dermis layer.

The transdermal perfusion of fluids for drug delivery has in recent years become an increasingly favoured alternative to intravenous or oral drug delivery. The technique has however found limited application because the epidermis (outer skin layer) forms an effective barrier to the perfusion of substances and in particular drugs having a large molecular size.

Various techniques have been proposed to enhance transdermal delivery including iontophoresis and the use as chemical enhancers. Mechanical stimulation for instance by ultrasound has also been used to enhance transdermal delivery. There remains a need however to provide a more effective transdermal technique particularly for peptides and hormones which hitherto have not been capable of being transdermally administered.

It is also known in the field of skin grafting to remove portions of the epidermis to expose the dermis layer of skin by the application of suction in which a partial vacuum of about 200 mm of mercury applied for a period of two or three hours has the effect of delaminating the epidermis from the dermis to form a blister containing a clear blister fluid. Such blisters have a roof which comprises the epidermis and can easily be removed for skin grafting.

According to the present invention there is disclosed apparatus for use in transdermal perfusion

of fluids through the skin of the human or animal body, the apparatus comprising a housing attachable to the body and having a contact surface which in use is held in contact with a portion of skin, the housing defining a chamber and the contact surface defining an aperture communicating with the chamber, and fluid supply means operable during a perfusion phase of operation of the apparatus to supply fluid to the chamber characterised in that the apparatus further comprises de-epithelialising means operable during a preparatory phase of operation of the apparatus to expose an area of dermis of the skin at a treatment site which is accessible via the aperture such that subsequently during the perfusion phase direct contact is made between fluid in the chamber and the dermis.

An advantage of such apparatus is that it allows a drug to be administered directly to an exposed dermis layer of the skin so that perfusion then proceeds in a manner which is not dependent upon any property of the epidermis. In particular the apparatus can be used on different parts of the body without needing to take account of the variation in thickness of the epithelium. A further advantage is that the micro circulation in the exposed dermis is found to be enhanced by the blister forming procedure and this hyperaemia is found to persist for some days after de-epithelialisation of the dermis and this effect is believed to assist the perfusion process.

The fluid may be a liquid, gel or cream.

The de-epithelialising means may comprise suction means operable to form a partial vacuum in the chamber during a blister forming period in which an area of epithelium of the skin at the treatment site is separated from the dermis.

An advantage of the use of such suction means is that the formation of a skin blister by suctioning is

a painless and minimally invasive procedure which heals rapidly and without leaving a scar. The healing process is such that the perfusion of drugs through the dermis does not become affected by the growth of a new epithelial barrier for at least four days after formation of the blister. This period can be extended by the application of suitable drugs which may be administered orally or otherwise.

Preferably the housing is cooperable with the skin to form a closed compartment of which the chamber constitutes at least a part and comprises sealing means operable between the contact surface and an annular area of skin peripheral to the treatment site whereby the partial vacuum is maintainable by substantially preventing the ingress of air during the blister forming period.

It is therefore not necessary for the chamber to remain connected to external apparatus providing suction so that a patient may be ambulatory and continue with normal physical activity during the two to three hours in which a suction blister is formed.

Conveniently the suction means comprises a cell defining a space within which a partial vacuum is formed and disrupting means operable to disrupt a membrane partitioning the space from the chamber.

It is therefore not necessary for the patient to be connected at any stage to any external suction device since partial vacuum may be introduced into the cell before attachment of the apparatus to the patient and partial vacuum subsequently applied to the chamber by subsequent disruption of the membrane.

The cell may be provided with a valve facilitating evacuation of air to create a partial vacuum within the space prior to operation of the disrupting means. A syringe or pump may be connected via the valve to the cell to provide a partial vacuum

and may then be disconnected before the apparatus is applied to the patient.

The apparatus may alternatively comprise expanding means operable to expand the volume of the chamber to thereby create a partial vacuum.

Preferably the apparatus comprises blister disruption means operable to open the suction blister by penetrating, bursting or removing the detached area of epithelium constituting a roof of the blister.

The apparatus may thereby remain in situ whilst the blister is opened to provide access to the de-epithelialised dermis.

An actuator may be provided to actuate the blister disruption means and also by subsequent movement of the actuator to actuate the fluid supply means.

The actuator may also be further operable to actuate the suction means.

A single actuator can therefore be used to operate the apparatus in its successive modes of operation.

Preferably the sealing means comprises an adhesive layer operable to sealingly secure the contact surface to an annular area of skin peripheral to the treatment site.

According to a further aspect of the present invention there is disclosed apparatus for use in the formation of a suction blister on the skin of the human or animal body, the apparatus comprising a housing attachable to the body and having a contact surface which in use is held in sealing contact with the skin, the housing defining a chamber and the contact surface defining an aperture communicating with the chamber, and the apparatus further comprising suction means operable to form a partial vacuum in the chamber and thereby form a suction blister at a

treatment site which is accessible via the aperture, characterised by the housing being cooperable with the skin to form a closed compartment of which the chamber constitutes at least a part and by comprising sealing means operable between the contact surface and the skin whereby the partial vacuum is maintainable by substantially preventing the ingress of air during a blister forming period.

An advantage of such apparatus is that it is not necessary for a patient to remain connected to a suction device during the suction blister forming period. The patient may therefore be ambulatory and may continue with normal physical activity.

The suction blister so formed may be used either for the sampling of blister fluid for subsequent analysis or the blister may be opened or removed to expose de-epithelialised dermis through which a drug may be perfused by the application of a suitable drug delivery mechanism.

Particular embodiments of the present invention will now be disclosed by way of example only and with reference to the accompanying drawings of which:-

Figure 1 is a sectioned elevation of a first apparatus for forming a suction blister;

Figure 2 is a sectioned elevation of a second apparatus for forming a suction blister and having an actuator pin;

Figure 3 is a sectioned elevation of the apparatus of Figure 2 showing the actuator pin in an advanced position in readiness to disrupt a suction blister;

Figure 4 is a sectioned elevation of the apparatus of Figures 2 and 3 showing the actuator pin in a further advanced position in which the blister is disrupted to expose the dermis;

Figure 5 is a sectioned elevation of a third

apparatus for forming a suction blister and having a pull ring actuator;

Figure 6 is a sectioned elevation of a fourth apparatus for forming a suction blister and having laterally disposed actuator pins;

Figure 7 is a sectioned elevation of a fifth apparatus for forming a suction blister and comprising a sprung bellows shown in a compressed state;

Figure 8 is a sectioned elevation of the apparatus of Figure 7 showing the sprung bellows in an expanded state;

Figure 9 is a sectioned elevation of a sixth apparatus for removing an area of epidermis by grinding;

Figure 10 is a sectioned elevation of a seventh apparatus for use in transdermal perfusion of a drug;

Figure 11 is a sectioned elevation of the apparatus of Figure 10 showing removal of a de-epithelialisation component of the apparatus;

Figure 12 is a sectioned elevation of the apparatus of Figures 10 and 11 in which the de-epithelialisation component is replaced by a drug delivery module;

Figure 13 is a sectioned elevation of an alternative drug delivery module for use with the apparatus of Figures 10 to 12;

Figure 14 is a sectioned elevation of an eighth apparatus for transdermal delivery of a drug including means for forming a suction blister, disrupting the blister and applying the drug directly to the exposed dermis;

Figure 15 is a sectioned elevation of a ninth apparatus having a cannula for drug delivery by injection;

Figure 16 is a sectioned elevation of the apparatus of Figure 15 showing the cannula extending

through the skin;

Figure 17 is a perspective view of a tenth apparatus for transdermal delivery of a drug and showing a suction chamber in its pre-use configuration;

Figure 18 is a perspective view of the apparatus of Figure 17 showing the introduction via a cannula of partial vacuum within the suction chamber;

Figure 19 is a perspective view of the apparatus of Figures 17 and 18 showing actuation of a blister disrupting fin;

Figure 20 is a perspective view of the apparatus of Figures 17 to 19 showing the opening of a valve admitting drug to the chamber;

Figure 21 is a sectioned elevation of an eleventh apparatus for transdermal drug delivery in its pre-use configuration;

Figure 22 is a sectioned elevation of the apparatus of Figure 21 showing the actuation of suction means to apply partial vacuum to the skin;

Figure 23 is a sectioned elevation of the apparatus of Figures 21 and 22 showing the release of partial vacuum following formation of a skin blister;

Figure 24 is a sectioned elevation of the apparatus of Figures 21 to 23 showing the disruption of the blister;

Figure 25 is a plan view of the apparatus of Figures 21 to 24;

Figure 26 is a side elevation of the apparatus of Figures 21 to 25;

Figure 27 is a section showing detail of a drug injection port of the apparatus of Figures 21 to 26;

Figure 28 is a section showing detail of a suction port valve of the apparatus of Figures 21 to 27;

Figure 29 is a section showing detail of an alternative drug injection port for use with the

apparatus of Figures 21 to 26;

Figure 30 is a perspective view of the apparatus of Figures 21 to 28 showing attachment to an arm of a patient;

Figure 31 is a perspective view of the apparatus of Figures 21 to 28 showing an alternative means of attachment to an arm of a patient;

Figure 32 is a perspective view of the apparatus of Figures 21 to 28 showing a further alternative means of attachment to the arm of a patient; and

Figure 33 is an elevation of the apparatus of Figure 32.

In Figure 1 a first apparatus 1 comprises a housing 2 of two-part construction. The housing 2 consists of a disc 3 and an evacuated cell 4 which is similarly of disc-shape and fits onto an upper surface 5 of the disc in use.

The disc 3 is formed of a rigid transparent plastics material and has a lower surface 6 which is coated with adhesive and prior to use is protected by a peel-off paper film 7. The disc 3 is centrally recessed to define a cup-shaped chamber 8 within a cylindrical formation 9 which projects upwardly of the upper surface 5. A cannula 10 projects from the cylindrical formation 9 in a direction away from the disc 3 so as to define a duct 11 communicating with the chamber 8. The cannula 10 is shown in Figure 1 in its pre-use configuration in which it is externally covered by a closed rubber sleeve 12.

The cell 4 is formed of a rigid transparent plastics material and encloses a space 13 which is provided at manufacture with a partial vacuum of 200mm of mercury.

The cell 4 has a lower face 14 which is centrally recessed by a cylindrical formation 15 within which the cylindrical formation 9 of the disc 3

is a sliding fit. The cylindrical formation 15 is closed by a disruptable membrane 16 formed of rubber.

The disc 3 is of 50mm diameter and defines a central aperture of 5mm diameter communicating with the chamber 8.

In use the paper film 7 is peeled off and the disc 3 is presented to an area of skin of the patient. The disc 3 is pressed onto the skin such that lower surface 6 is adhesively secured against the skin and forms an airtight seal. The cell 4 is advanced onto the disc 3 such that cylindrical formation 15 fits over the cylindrical formation 9 and the cannula 10 ruptures both the rubber sleeve 12 and membrane 16 to establish communication via the duct 11 between the space 13 and the chamber 8. A partial vacuum is thereby applied within the chamber 8 to an area of skin within aperture 18. The apparatus 1 is held in this position adhesively for two to three hours during which time a suction blister is formed within the chamber 8. Formation of the blister can be observed by inspection through the transparent material forming the cell 4 and disc 3. The apparatus is then removed from the skin by first removing the cell 4 to release the partial vacuum within chamber 8 and then peeling the disc 3 away from the skin.

The exposed blister may then be broken or removed to gain access for transdermal delivery of a drug to the exposed skin dermis or the blister fluid may be sampled for subsequent analysis.

A second apparatus 20 shown in Figure 2 comprises a housing 21 which includes a transparent disc-shaped base 22 defining a contact surface 23. The contact surface 23 has an adhesive coating which is protected prior to use by a peel-off paper film 24. The contact surface 23 is centrally recessed by

a cylindrical formation 25 defining a cylindrical chamber 26, the contact surface 23 defining a circular aperture 27 of 5mm diameter communicating with the chamber 26. The chamber is closed at its other end by a disruptable rubber membrane 28.

The housing 21 further comprises a cell 29 of transparent plastics material which is closed by membrane 28 to enclose a sealed space 30. The space 30 is evacuated at manufacture to provide a partial vacuum of 200mm of mercury.

An actuator pin 31 projects sealingly through an outer wall 32 of cell 29. Actuator pin 31 is axially movable towards the membrane 28 so as to form a central puncture in use.

In use the film 24 is peeled off and the contact surface 23 is adhesively secured to the skin of the patient so as to form an airtight seal. The chamber 26 is then closed by an area of skin defined within the aperture 33. Actuator pin 31 is then advanced so as to rupture the membrane 28 and air moves through the ruptured membrane to equalise pressure in the space 30 and chamber 26. A partial vacuum is thereby applied to the area of skin exposed within the aperture 33. The chamber 26 and the space 30 together constitute a closed compartment in which a partial vacuum is maintained so long as the ingress of air is prevented by the airtight seal between the contact surface and the skin. The apparatus 20 is left in situ for a period of about two hours during which time the formation of a suction blister 34 is observed through the transparent housing 21 as shown in Figure 3. In Figure 3 the actuator pin 31 is shown in an orientation in which it is rotated through 90° relative to the position shown in Figure 2 thereby revealing cutting edges 35 which disrupt the blister 34 as shown in Figure 4 when the actuator pin

is further advanced.

The contents of the blister 34 may be sampled and analysed or a skin patch (not shown) may be applied over the site of the broken blister to apply a liquid drug to be perfused through the exposed dermis.

A third apparatus 40 is shown in Figure 5 and will be described using corresponding reference numerals to those of Figures 2, 3 and 4 where appropriate for corresponding elements.

Apparatus 40 similarly has a transparent housing 21 with a cell 29 enclosing an evacuated space 30 and suction is applied through aperture 27 in contact surface 23 by creating a partial vacuum in chamber 26 by disrupting a membrane 28. The apparatus 40 includes a pull-ring actuator 41 to which is attached a first end 42 of a wire 43 of which a second end 44 is anchored in the membrane 28. The wire 43 is enclosed within a sheath 45 which is sealed to both the outer wall 32 of the cell 29 and the membrane 28.

In use the pull-ring actuator 41 is pulled to displace the wire 43 so that the second end 44 is pulled through the membrane 28 leaving a hole through which air flows between the chamber 26 and space 30. A partial vacuum is thereby applied to the chamber 26 for the formation of a skin blister. The partial vacuum then persists in the closed compartment constituted by chamber 26 and space 30 so long as an airtight seal across the aperture is provided by adhesive contact with the skin.

A fourth apparatus 50 is shown in Figure 6 and will be described using corresponding reference numerals to those of Figure 2 where appropriate for corresponding elements.

Apparatus 50 comprises a transparent housing 21 having a contact surface 23 and an evacuated cell 29. A cylindrical formation 25 defines a chamber 26

which is closed by adhesion of the contact surface 23 to an area of skin and partial vacuum within the chamber 26 is then applied by disrupting side walls 51 of the cylindrical formation 25 by means of laterally extending actuator pins 52 and 53. Operation of the apparatus 50 is in other respects similar to that of apparatus 20.

In Figure 7 a fifth apparatus 60 comprises a disc-shaped base 61 defining a central aperture 62 which communicates directly with a chamber 63 defined by a bellows 64. The bellows 64 is biassed by coil springs 65 and 66 into an extended position as shown in Figure 8. The apparatus 60 is normally stored in its compressed state as shown in Figure 7 and the base 61 defines a contact surface 67 which is adhesively coated and is provided pre-use with a protective film 68. The film 68 closes aperture 61 in this condition to prevent ingress of debris during storage.

The bellows 64 is clamped in its compressed condition by means of a clamp (not shown) and an actuator (not shown) is provided to release the clamp to allow the bellows to expand to its expanded configuration shown in Figure 8.

In use the film 68 is removed and the contact surface 67 applied to the skin so that aperture 62 is closed in airtight manner by an area of skin. The actuator is operated to unclamp the bellows 64 and the bellows expand by spring action to thereby increase the volume of chamber 63 and this results in the creation of a partial vacuum which is applied to the area of skin exposed by aperture 62. The apparatus 60 is left in situ for a period of about two hours and may then be removed first by compressing the bellows to its original shape to remove the partial vacuum and then peeling off the contact surface from the skin. The blister may then be broken or removed and a

transdermal skin patch applied to the exposed dermis.

A sixth apparatus 70 is shown in Figure 9 and comprises a disc 71 which is axially mounted on a shaft 72. The disc 71 has a flat contact surface 73 from which a plurality of sharp edged protrusions 74 project towards the skin. The protrusions 74 have a height corresponding to the depth of epidermis and in use the contact surface is placed against the skin and the disc rotated by means of shaft 72 to thereby form incisions in the epidermis. The apparatus 70 is then removed and a skin patch containing a drug is then applied to the area of skin in which the incisions are formed.

A seventh apparatus 80 is shown in Figures 10, 11 and 12 and comprises a housing 81 consisting of an annular frame 82 which is adhesively secured to an area of skin 83 in use. A de-epithelialising apparatus 84 is releasably locatable within the annular frame 82 and in Figures 10 and 11 the de-epithelialising apparatus 84 is of the type described above with reference to Figures 2, 3 and 4 in which a suction blister is formed and ruptured by actuation of an actuator pin 85. In Figure 10 the de-epithelialising apparatus 84 is shown in situ prior to use. In Figure 11 the de-epithelialising apparatus is shown separated from the frame 82 after formation and rupturing of the blister (not shown). Figure 12 shows a drug delivery module 86 located within the frame 82 following removal of the de-epithelialising apparatus 84. The drug delivery module 86 comprises a disc-shaped casing 87 having a central drug compartment 88 which includes a semi-permeable membrane 89 through which the drug exudes at a predetermined rate. (Detail of the ruptured blister is omitted from Figure 12).

The casing 87 is configured to be a close fit

within the frame 82 and to locate the membrane 89 over the location of the area of skin which is de-epithelialised by the apparatus 84.

The diameter of the membrane 89 is greater than the diameter of the de-epithelialised skin patch to take account of any errors in positioning.

The apparatus of Figures 10 to 12 may alternatively utilise the apparatus of Figure 9 in achieving de-epithelialising of the skin, the apparatus 70 being located within the frame 82 and removed prior to insertion of drug delivery module 86.

An alternative drug delivery module 90 is shown in Figure 13 and comprises a reservoir 91 containing a volume of drug, the reservoir being held by an annular support 92 in proximity with skin surface 93. The support 92 defines a narrow bore connecting tube 94 communicating between the reservoir 91 and a recess 95 which is defined by the support and overlays the de-epithelialised skin area. Liquid drug is progressively fed by capillary action through the connecting tube 94 into the recess and hence is perfused through the exposed dermis.

The flow of liquid through the connecting tube may be aided by the application of positive pressure to the reservoir 91.

In Figure 14 an eighth apparatus 100 for the transdermal delivery of a drug comprises a transparent housing 101 with a disc-shaped base 102. A contact surface 103 is adhesively coated so as to adhere to a skin surface and the base defines a central aperture 104 communicating with a chamber 105 formed by a cylindrical formation 106.

The cylindrical formation 106 is closed at one end by a frangible membrane 107 which initially separates the chamber 105 from an evacuated space 108 provided by a cell 109 of the housing 101.

The frangible membrane 107 is disruptable by means of an actuator pin 110 of the type described above with reference to Figures 2, 3 and 4 so that actuation of the pin 110 ruptures the membrane to introduce partial vacuum into the chamber 105 during a blister forming period. Further actuation of the pin 110 advances the pin to a position in which it will disrupt the blister to expose the dermis within the chamber 105.

Apparatus 100 also comprises an integrally formed drug reservoir 111 which is normally sealed by a frangible plug 112. A drug release actuator 113 is provided for breaking the plug 112 and allowing the drug to flow into the chamber 105.

In use the apparatus 100 is placed on the skin such that adhesion between the contact surface 103 and skin provides an airtight seal across the aperture 104. The actuator pin is then advanced to disrupt the membrane 107 so that a partial vacuum is produced in the chamber 105 to form a blister. The cell and chamber together constitute a closed compartment sealed by the area of skin and in which partial vacuum persists during a blister forming period. The blister is then ruptured by further actuation of actuator pin 110 and the drug release actuator 113 is then operated to allow drug into the chamber 105. De-epithelialised dermis exposed by rupturing the blister is then exposed to the drug and transdermal perfusion then proceeds.

In Figure 15 a ninth apparatus 120 includes an apparatus for transdermal drug delivery such as that described with reference to Figure 14 (details of such transdermal apparatus are not shown in Figure 15) and additionally includes an injection device 121 which is operable to inject via a cannula 122 an initial dose of drug prior to de-epithelialisation and transdermal

delivery by means of the transdermal apparatus using an adjacent patch of skin. Such immediate administration of a dose is useful in administering pain relief for example or control of premature muscle contractions of the uterus during pre-term labour.

The injection device 121 comprises an additional suction cup 123 defining a suction chamber 124 to which suction is applied to immediately draw skin into the chamber as shown in Figure 16. The cannula 122 is located within the chamber in a position such that skin drawn into the chamber by suction is penetrated. Drug is then injected through the cannula from a reservoir 125 on release of a valve 126. Drug within the reservoir 125 is pressurised by means of an expanding device 127 placed in contact with the reservoir 125 which is formed of a deformable material so as to be collapsible.

A tenth apparatus 130 shown in Figure 17 comprises a housing 131 having an annular contact surface 132 defining an aperture 133. The housing 131 is centrally recessed to define a chamber 134 communicating with the aperture.

The housing 131 incorporates an annular drug reservoir 135 peripherally disposed relative to the aperture 133 and includes an evacuated cell 136 which is isolated from the chamber 134 prior to use by a disruptable membrane 137.

The housing 131 has an actuator cap 138 which is movable relative to a base portion 139 which includes the contact surface 132.

Apparatus 130 is arranged to provide for the formation and disruption of a suction blister and for subsequent drug delivery to the exposed dermis by successive actuation of the actuator cap 138.

The housing 131 is initially secured to a patch of skin such that the aperture 133 is closed in a

sealed manner by an area of skin through which drug is to be transdermally delivered. The housing 131 is secured by means of a peripheral support frame (not shown).

As shown in Figure 18 the actuator cap 138 is pressed towards the base portion 139 so as to advance a cannula 140 so as to penetrate the membrane 137 and place the chamber 134 in communication with the evacuated cell 136. A partial vacuum is thereby created within the chamber 134 and the partial vacuum persists during a blister forming period by virtue of the contact surface 132 being sealed against the skin.

After a period of two hours the actuator cap 138 is rotated through 45° as shown in Figure 19 in response to which motion air is admitted to the chamber 134 through a release valve (not shown) so as to restore atmospheric pressure and a blister disrupting fin 141 moves into the chamber 134 and breaks or removes the roof of the blister formed within the chamber. The fin 141 includes an absorbent layer 142 which absorbs blister fluid released by this motion.

The actuator cap 138 is again further advanced as shown in Figure 20 through a rotational movement of 45° and this further motion opens a valve to release a liquid drug from the reservoir 135 through an outlet 143 into the chamber 134.

Transdermal perfusion of the drug through the exposed dermis of the skin then proceeds.

An eleventh apparatus 150 shown in Figure 21 also includes an actuator cap 151 which provides successive operations of blister formation, blister disruption and drug release by successive stages of movement of the cap relative to a base portion 152 of a housing 153. The housing 153 includes a disc portion 154 having a flat disc-shaped contact surface

192 defining a central aperture 155 of 5mm diameter. The aperture 155 communicates with a chamber 156 defined by a cylindrical formation 157 projecting upwardly of the disc portion.

The housing 153 includes a cell 158 bounded on one side by the disc portion 154 and defining a closed space 159. The housing 153 also includes a drug reservoir 160 which is separated from the space 159 by a partition 161 extending parallel to the disc portion 154.

The volume of the drug reservoir 160 is variable by movement of a piston 162 which is movable towards the partition 161 to reduce the volume of the reservoir for the purpose of expelling liquid drug.

The housing 153 is cylindrical in shape and the actuator cap 151 is similarly cylindrical and overlays the housing, the housing and cap having cooperating screw threads 163 whereby rotation of the cap relative to the housing advances the cap towards the disc portion 154.

A hollow needle 164 is mounted axially within the cap 151 such that rotation of the cap produces axial movement of the needle relative to the housing.

In Figure 21 the apparatus 150 is shown in its initial rest position in which the needle 164 projects sealingly through the piston 162.

The partition 161 includes a central orifice 165 which is normally sealed by a rubber plug 166. The rubber plug 166 is in axial alignment with the needle 164 and with a membrane seal 167 forming part of the cylindrical formation 157 and normally separating the chamber 156 from the space 159 within cell 158.

The piston 162 is biassed in a direction towards the partition 161 by means of a coil spring 168 and the piston is restrained against axial movement by means of a catch 169 which is releasable by rotation

of the cap 151 in a manner described below.

The hollow needle 164 has a side hole 170 which in the rest position shown in Figure 29 is located above the piston 162 so as to be outside of the drug reservoir 160. The piston is provided with upper and lower sliding seals 210,211 respectively which "bracket" the side hole 170 and prevent entry of air.

The needle 164 also has an indentation 171 located intermediate the side hole 170 and the needle tip 172.

Rotation of the piston 162 relative to the base portion 152 is prevented by means of a locating pin 173 which is received in a cooperating recess 174 of the piston.

The cell 158 is evacuated to have a partial vacuum of 200mm of mercury.

The apparatus is prepared for use by removing a protective film to expose an adhesive coated disc portion 154, the cell 158 being evacuated and the drug reservoir 160 being initially empty.

In use, the housing 153 is attached to the skin of the user such that the disc portion 154 is adhesively sealed to an annular area of skin 193 peripheral to a treatment site 196. Central aperture 155 is thereby sealed against ingress of air which thereby closes the chamber 156. Suction is applied at the treatment site 196 by actuation of the cap 151 so as to advance the needle 164 through both the rubber plug 166 and the membrane seal 167. The membrane seal 167 is formed of a frangible material which fractures and provides for the passage of air between the space 159 and the chamber 156 thereby reducing the pressure within the chamber. The rubber plug 166 maintains sealing engagement with the needle 164 so that no air enters the space 159 from the reservoir 160. Air cannot enter the chamber 156

through the needle 164 since the side hole 170 remains sealed by the seals 210,211.

A partial vacuum is maintained within the closed compartment constituted by the space 159 and the chamber 156 during a blister forming period, the ingress of air being prevented by an adhesive seal between the disc portion 154 and the annular portion of skin 193.

The formation of a blister is illustrated in Figure 22 which shows the position of the needle during the blister forming period. The blister consists of a raised portion of epithelium 195 which is 'delaminated' from the dermis 194 to which it is normally attached.

Once a blister has been formed after a period of two hours a further rotational movement of the cap 151 is required to further advance the needle 164 to the venting position shown in Figure 23 in which the indentation 171 comes into registration with the rubber plug 166 thereby allowing air from the reservoir 160 to enter the space 159 to restore atmospheric pressure.

At this stage a quantity of drug is inserted into the reservoir 160 through a drug insertion port 175 of the type shown in Figure 28. Although not shown in Figure 21 the insertion port 175 is located so as to provide a means of injecting liquid drug through the housing into the reservoir 160.

The drug insertion port 175 comprises a duct 176 communicating with the reservoir 160 and closed by a self-healing rubber bung 177 through which a syringe needle is insertable.

After filling the reservoir 160 with a liquid drug a further movement of the actuator cap 151 rotates the cap to a position in which the side hole 170 is located within the reservoir 160 and at the

same time the catch 169 operates to release the piston 162. Under the action of the spring 168 the piston 162 pressurises liquid within the reservoir 160 which flows into the needle 164 through the hole 170 and emerges from the needle tip 172 into the chamber 156. By this further advancement of the needle the blister 178 is ruptured so that drug within the chamber 156 comes into contact with the exposed dermis 179 so that transdermal delivery of the drug is commenced.

As shown in Figure 24 the needle 164 includes a microporous filter 180 adjacent the needle tip 172 by means of which the flow of liquid into the chamber 150 is restricted. This slows the rate of release of drug into the chamber 156 and ensures a gradual release of drug t a predetermined rate.

The housing 153 is held in situ for a period during which transdermal delivery proceeds and this period may extend to four days by which time the self-healing of the epidermis will begin to provide a barrier preceding direct access to the dermis.

The construction of the catch 169 is illustrated in Figure 25 which shows three circumferentially spaced feet 181 which are connected to the piston 162 by legs 182 such that the feet normally engage a supporting annular track 183 attached to the cap 151. The track 183 is provided with cut-outs 184 into which the feet 181 fall to release the catch 169 when the cap is rotated to its final position.

During rotation of the cap 151 relative to the base portion 152 the cap is advanced axially by screw action. In order to prevent the piston 162 advancing until released by the catch 169 the track 183 is ramped to provide a compensating axial movement of the piston relative to the cap so that the piston remains stationary relative to the base portion 152.

Rotation of the cap 151 relative to the base portion 152 is stepped by use of suitable snap fitting detents and corresponding recesses (not shown) on the cap and base portion respectively. As shown in Figure 26, suitable markings are provided on the cap 151 and base portion 152 to indicate the sequential steps of rotation.

The drug insertion port 175 may be replaced by a drug filling port 185 of the type shown in Figure 29 in which a duct 186 is normally closed by a hinged snap fitting closure 187. Drug is therefore introduced into the reservoir 160 by opening the closure 187, pouring the drug in and replacing the closure.

The space 159 may be provided with a partial vacuum at manufacture or alternatively the partial vacuum within the space 159 may be produced immediately before use by withdrawing air through a suction port 188 of the type shown in Figure 28. Suction port 188 comprises a duct 189 communicating with the space 159 via a non-return valve 190, the duct 189 being defined by a Luer connector 191 into which the hub of a syringe can be sealingly inserted. Suction created by reverse actuation of the syringe will thereby withdraw air through the non-return valve 190 from the space 159 to create a partial vacuum. The syringe is withdrawn from the connector 191 and the cell 158 is then sealed automatically by action of the valve 190 before attachment of the housing 153 to the skin.

The housing 153 may be attached to the skin of an arm or leg in the manner shown in Figure 29 where an adhesive strip 200 extends around the limb 201. Alternatively as shown in Figure 30 an annular adhesive film 202 may attach the housing 153 to a localised area of skin thereby contributing to the

airtight seal formed between the disc portion 154 and the skin but without any further means of holding the housing in situ.

As shown in Figure 32 the arrangement of Figure 30 can be supplemented by the addition of a strap fastened using a hook-loop fastener 203 as illustrated in Figure 33.

In the above embodiments the adhesive used in contact with the skin may be of a hydrocolloidal type composed of pectin and gelatine or may alternatively be composed of acrylic or silicon. In each case the apparatus may be supplied with the adhesive covered in a protective sheet which also seals the aperture formed in the contact surface and the entire assembly can be sterilised in readiness for use.

The fifth apparatus 60 of Figures 7 and 8 may be provided with alternative means of expanding the chamber 63. For example a screw type arrangement or piston arrangement may be used to expand the enclosed chamber.

The contact surface may be sealed to the skin other than by the use of adhesive if required. For example the contact surface may be provided with projecting ribs which sealingly engage the skin surface and in such an arrangement the apparatus should be held firmly in place for example by straps.

Apparatus in accordance with the present invention may be provided with more than one evacuated cell to allow the partial vacuum to be re-established for example for the purpose of removing a self-healed epidermal barrier or to remove by suction any blister fluid within the chamber.

It may be desirable to provide apparatus in which the contact surface is interchangeable to provide apertures of different size.

The size of the de-epithelialised area of skin

may also be stretched by applying stretching means to the surrounding skin.

In the examples referred to above the aperture size of 5mm may be varied typically in the range 1mm to 10mm.

The drug may be applied in a form producing slow release, for instance by reversible binding in absorbent biodegradable starch particles, polymer(s), in non-biodegradable polysaccharide spheres, or in microcapsules consisting for instance partly of lipids or polymers of different types which may break or disintegrate slowly in biological fluids.

The drug may be applied in so-called pro-drug form, allowing it to pass through the tissue into the blood with minimal break-down (this being an important aspect in peptide delivery).

The re-epithelialisation of the drug delivery site can be delayed for instance by applying a steroid drug in addition to the therapeutic agent. Other means, for instance addition of antibodies to epithelial cells, may be used for the same purpose. The apparatus could be pre-loaded with such an agent, it could be added to the drug solution or taken by other routes.

The apparatus of Figures 1 to 6, 14 to 20 may be provided with a suction valve of the type described with reference to Figure 28.

The apparatus of Figures 17 to 20 and of Figures 21 to 26 may be modified to include an expansion means of the type described with reference to Figure 7. The apparatus may also optionally include a valve for interrupting the delivery of drug in use.

In the above embodiments reference is made to the delivery of drugs in liquid form. The apparatus may also be used to deliver gels and creams with suitable modification where appropriate.

Throughout the description and claims the term perfusion should be understood to encompass both the partial and complete diffusion of a fluid through body tissue i.e. including the partial diffusion of a fluid in which certain molecules contained in the fluid are diffused through tissue leaving a residue of undiffused fluid.

CLAIMS:

1. Apparatus (150) for use in transdermal perfusion of fluids through the skin of the human or animal body, the apparatus comprising a housing (153) attachable to the body and having a contact surface (192) which in use is held in contact with a portion of skin (193), the housing defining a chamber (156) and the contact surface defining an aperture (155) communicating with the chamber, and fluid supply means (164) operable during a perfusion phase of operation of the apparatus to supply fluid to the chamber characterised in that the apparatus further comprises de-epithelialising means (158,156) operable during a preparatory phase of operation of the apparatus to expose an area of dermis (194) of the skin at a treatment site (196) which is accessible via the aperture such that subsequently during the perfusion phase direct contact is made between fluid in the chamber and the dermis.

2. Apparatus as claimed in claim 1 wherein the de-epithelialising means comprises suction means operable to form a partial vacuum in the chamber during a blister forming period in which an area of epithelium (195) of the skin of the treatment site is separated from the dermis.

3. Apparatus as claimed in claim 2 wherein the housing is cooperable with the skin to form a closed compartment (158,156) of which the chamber constitutes at least a part and comprises sealing means operable between the contact surface an annular area of skin peripheral to the treatment site whereby the partial vacuum is maintainable by substantially preventing the ingress of air during the blister forming period.

4. Apparatus as claimed in claim 3 wherein the suction means comprises a cell (158) defining a space within which a partial vacuum is formed and disrupting means (164) operable to disrupt a membrane (167) partitioning the space from the chamber.

5. Apparatus as claimed in claim 4 wherein the cell is provided with a valve (190) facilitating evacuation of air to create a partial vacuum within the space prior to operation of the disrupting means.

6. Apparatus as claimed in claim 3 comprising expanding means (64) operable to expand the volume of the chamber (63) to thereby create a partial vacuum.

7. Apparatus as claimed in any of claims 3 to 6 further comprising blister disruption means (164) operable to open the suction blister by penetrating or removing the detached area of epithelium constituting a roof of the blister.

8. Apparatus as claimed in claim 7 comprising an actuator (151) operable to sequentially actuate the suction means, the blister disruption means and by subsequent movement of the actuator to actuate the fluid supply means.

9. Apparatus as claimed in claim 8 wherein the actuator is operatively connected to a tubular member which is movable longitudinally in response to actuator movement so as to disrupt the membrane partitioning the space from the chamber to thereby initiate the blister forming period, the member being further longitudinally movable to a position in the chamber in which it disrupts the blister and the

member further defining a longitudinal bore (197) through which fluid is supplied to the chamber during the perfusion phase.

10. Apparatus as claimed in any of claims 3 to 9 wherein the sealing means comprises an adhesive layer operable to sealingly secure the contact surface to an annular area of skin peripheral to the treatment site.

11. Apparatus as claimed in any preceding claim wherein the fluid supply means includes flow restricting means (180) operable to restrict the flow of fluid into the chamber to a predetermined rate.

12. Apparatus for use in the formation of a suction blister on the skin of the human or animal body, the apparatus comprising a housing (21) attachable to the body and having a contact surface (23) which in use is held in sealing contact with the skin, the housing defining a chamber (26) and the contact surface defining an aperture (27) communicating with the chamber, and the apparatus further comprising suction means (29) operable to form a partial vacuum in the chamber and thereby form a suction blister at a treatment site which is accessible via the aperture, characterised by the housing being cooperable with the skin to form a closed compartment (29,26) of which the chamber constitutes at least a part and by comprising sealing means operable between the contact surface and an annular portion of skin peripheral to the treatment site whereby the partial vacuum is maintainable by substantially preventing the ingress of air during a blister forming period.

13. Apparatus as claimed in claim 12 wherein the suction means comprises a cell (29) defining a space (30) within which a partial vacuum is formed and disrupting means (31) operable to disrupt a membrane (28) partitioning the space from the chamber.

14. Apparatus as claimed in claim 13 wherein the cell is provided with a valve (190) facilitating evacuation of air to create a partial vacuum within the space prior to operation of the disrupting means.

15. Apparatus as claimed in claim 12 comprising expanding means (64) operable to expand the volume of the chamber to thereby create a partial vacuum.

16. Apparatus as claimed in any of claims 12 to 15 further comprising blister disruption means (31,35) operable to open the suction blister by penetrating, bursting or removing the detached area of epithelium constituting a roof of the blister.

17. Apparatus as claimed in claim 16 wherein the disrupting means of the suction means comprises a member (31) extending into the closed compartment and connected to an actuator located externally of the compartment, the member being movable from a rest position into a first position in which the member actuates the suction means and a second position in which the member disrupts the blister.

18. Apparatus as claimed in any of claims 12 to 16 wherein the sealing means comprises an adhesive layer operable to sealingly secure the contact surface to an annular area of skin peripheral to the treatment site.

19. A method of transdermal perfusion of fluids through the skin of the human or animal body, comprising the steps of attaching a housing (153) to the body such that a contact surface (192) of the housing is held in contact with a portion of skin, the housing defining a chamber (156) and the contact surface defining an aperture (155) communicating with the chamber, and operating a fluid supply means (164) during a perfusion phase of operation to supply a quantity of fluid to the chamber characterised by further comprising the step of de-epithelialisation of the skin during a preparatory phase of operation of the apparatus to expose an area of dermis (194) of the skin at a treatment site (196) which is accessible via the aperture such that subsequently during the perfusion phase direct contact is made between fluid in the chamber and the dermis.

20. A method as claimed in claim 19 wherein the step of de-epithelialisation comprises the operation of suction means to form a partial vacuum in the chamber during a blister forming period in which an area of epithelium of the skin at the treatment site is separated from the dermis and subsequently penetrating or removing the detached area of epithelium constituting the roof of the blister.

21. A method as claimed in claim 20 wherein the housing is cooperable with the skin to form a closed compartment of which the chamber constitutes at least a part and including the step of applying sealing means between the contact surface and an annular area of the skin peripheral to the treatment site whereby the partial vacuum is maintained by substantially preventing the ingress of air during the

blister forming period.

22. A method of forming a suction blister on the skin of the human or animal body comprising the steps of attaching a housing to the body such that a contact surface of the housing is held in sealing contact with the skin, the housing defining a chamber and the contact surface defining an aperture communicating with the chamber, and operating suction means to form a partial vacuum in the chamber and thereby form a suction blister at a treatment site which is accessible via the aperture, characterised by the housing cooperating with the skin to form a closed compartment of which the chamber constitutes at least a part and by including the step of applying sealing means between the contact surface and an annular area of the skin peripheral to the treatment site prior to operation of the suction means whereby the partial vacuum is subsequently maintained by substantially preventing the ingress of air during a blister forming period.

23. A method as claimed in claim 22 including the further step of evacuating air from a cell defined by the housing to form a partial vacuum therein and sealing the cell prior to attaching the housing to the body, and operating the suction means to place the chamber in communication with the cell to thereby form a partial vacuum in the chamber.

FIG. 1.

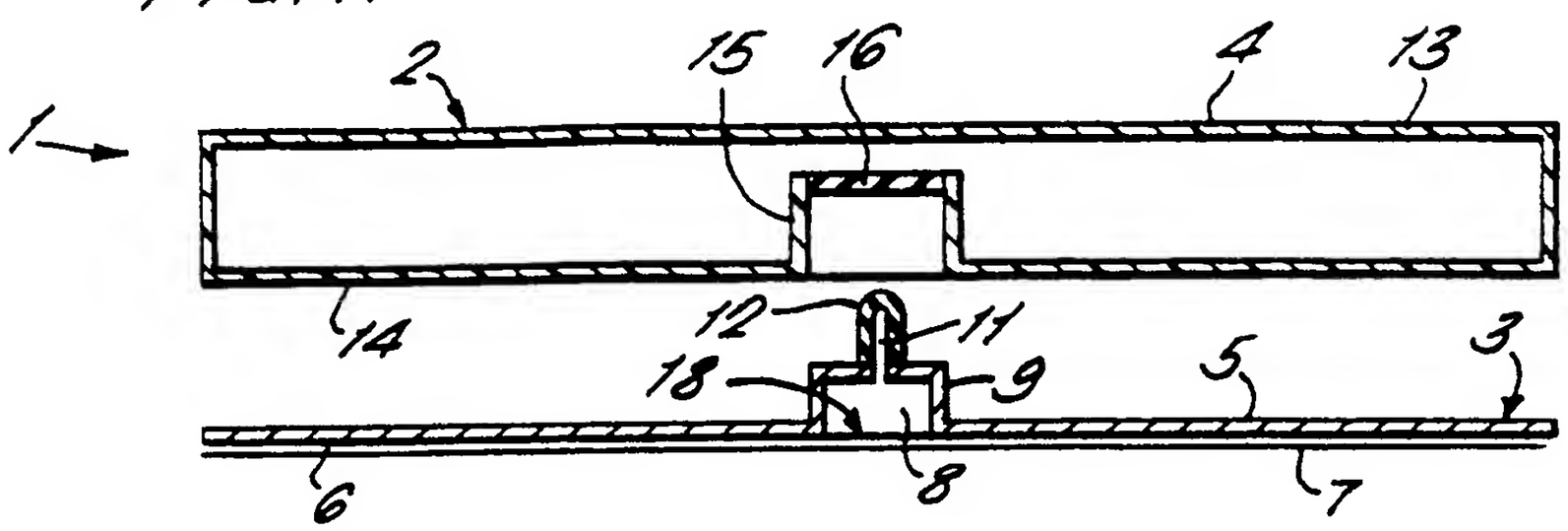


FIG. 2.

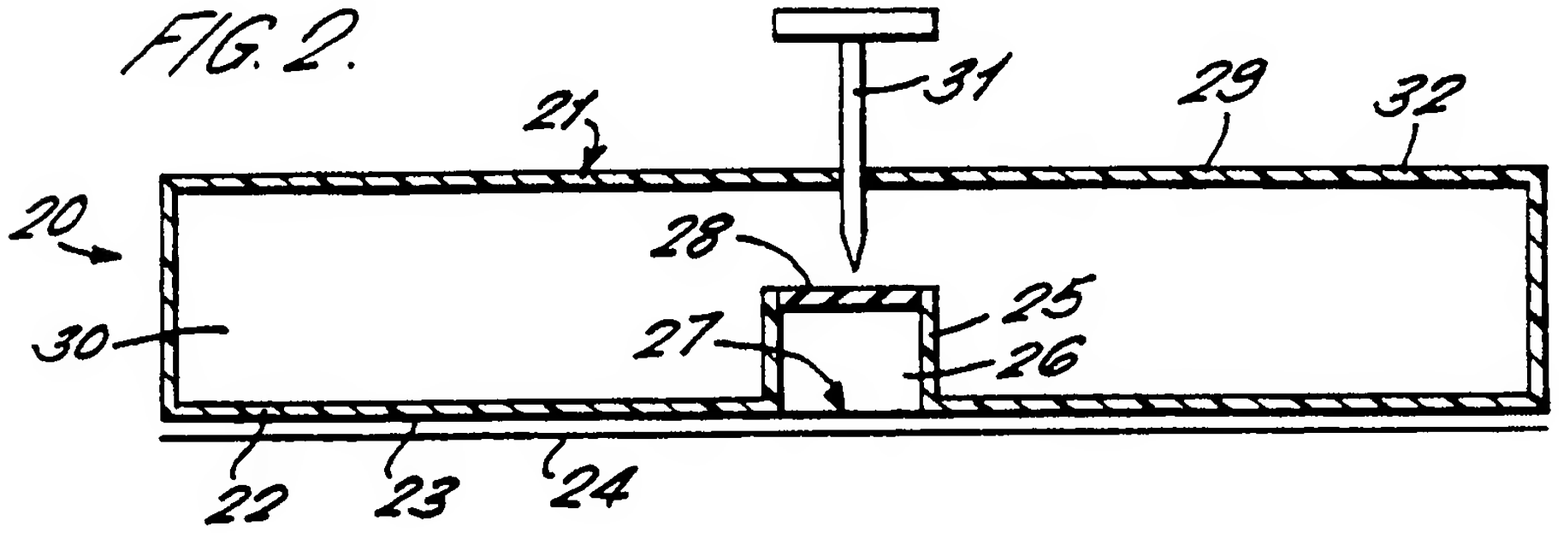


FIG. 3.

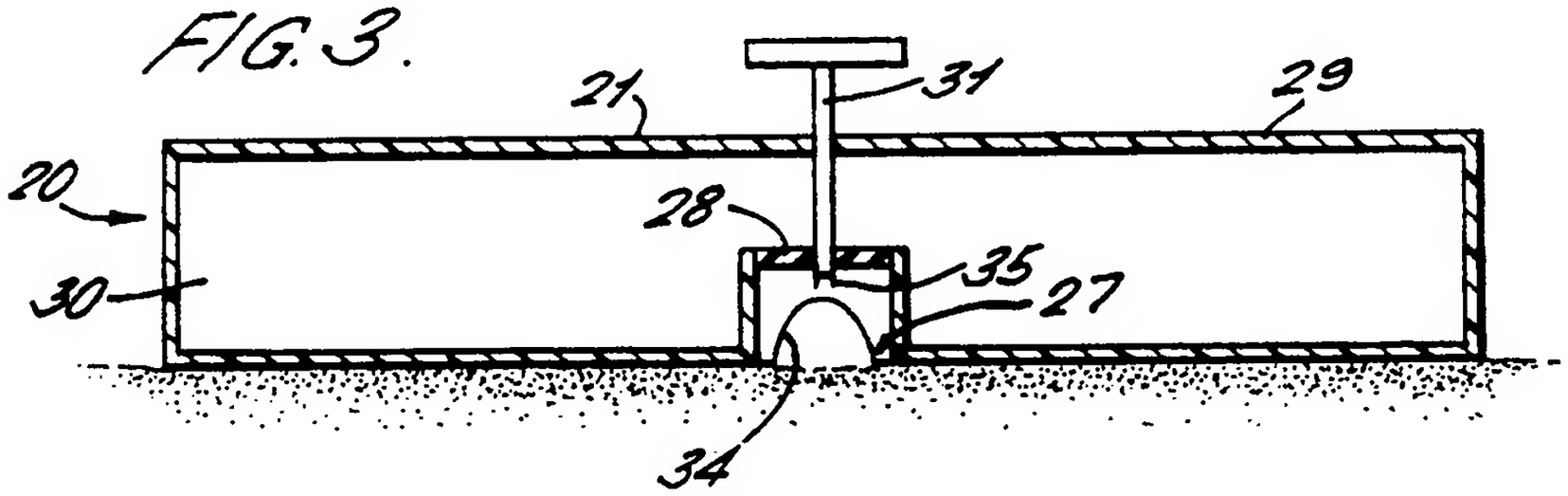


FIG. 4.

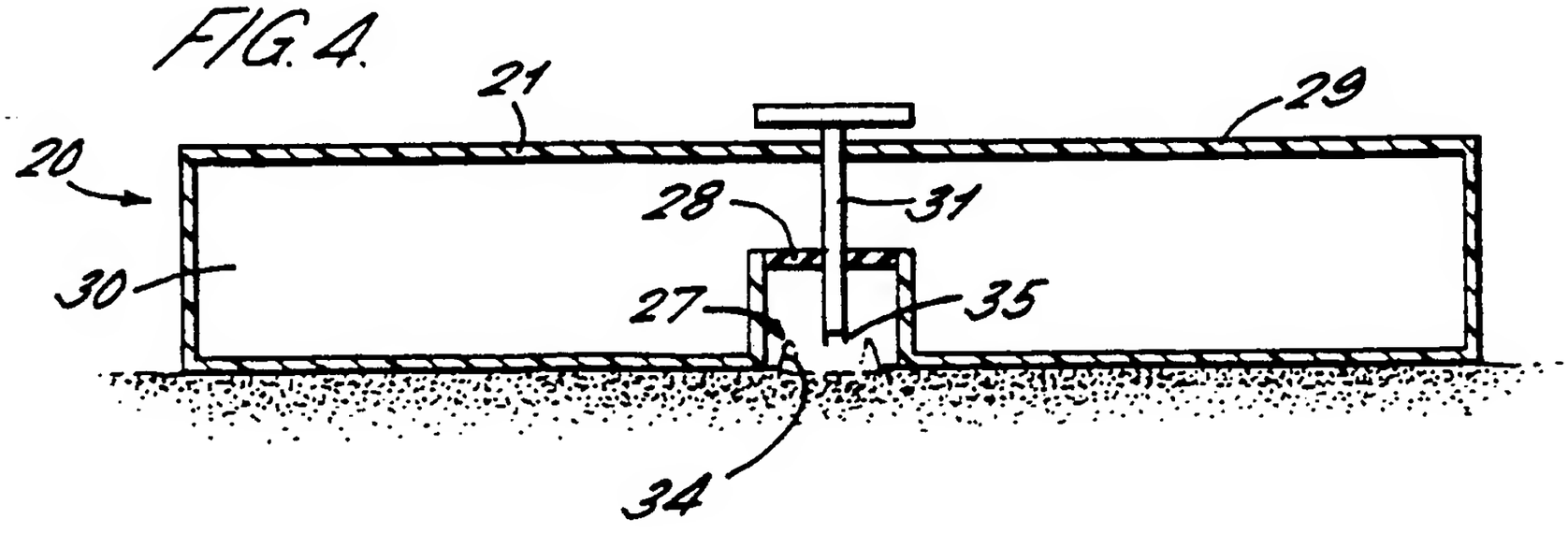


FIG. 5.

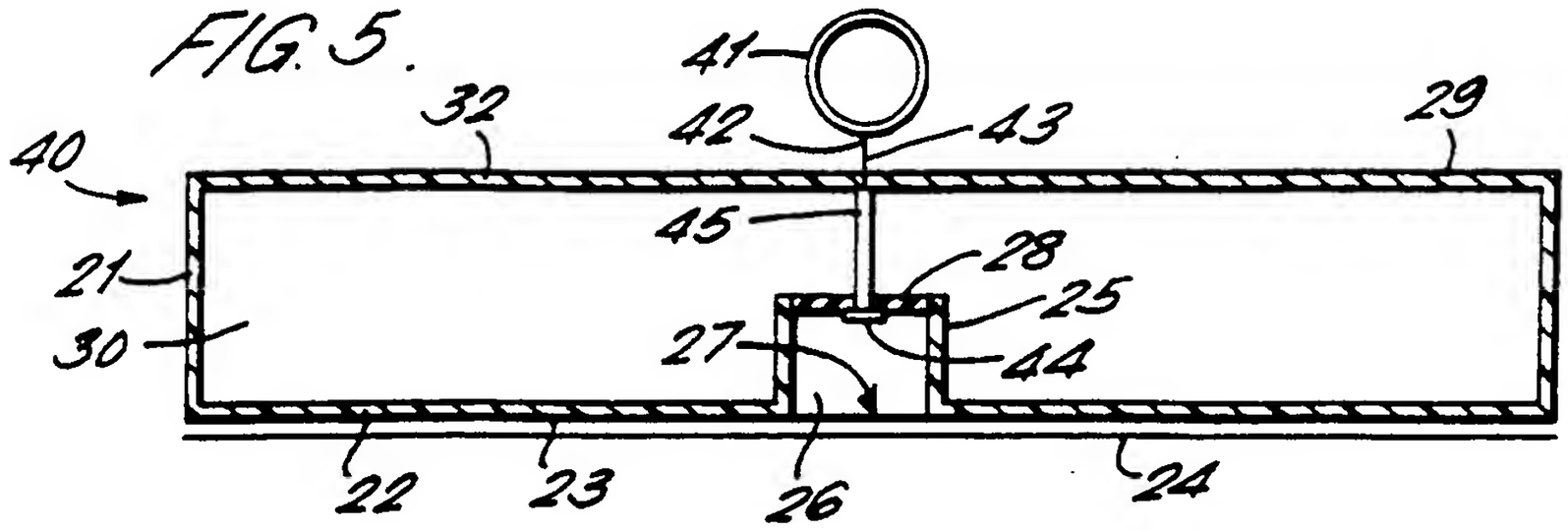


FIG. 6.

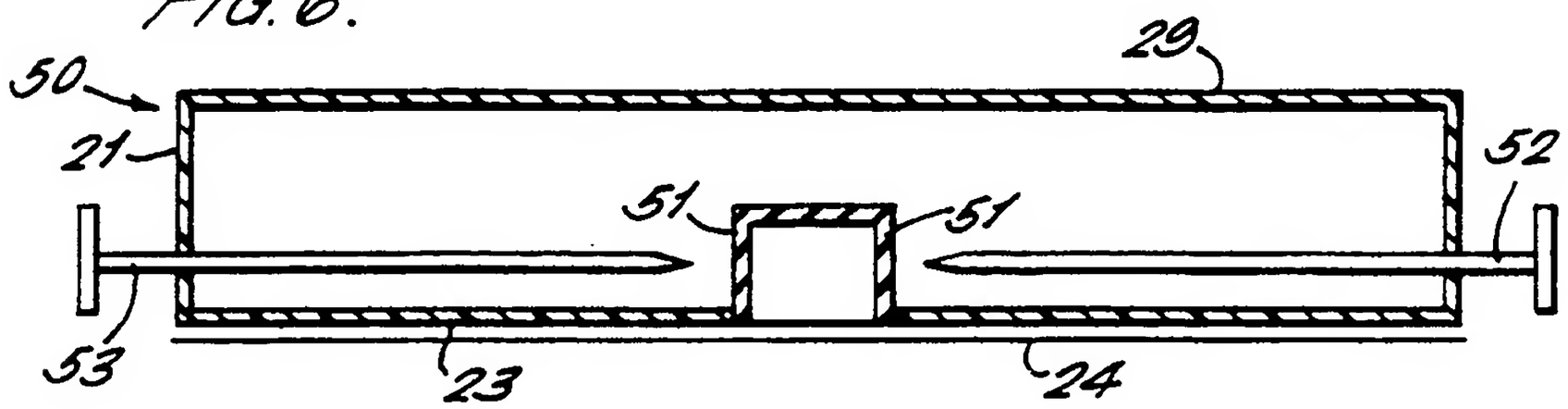


FIG. 7.

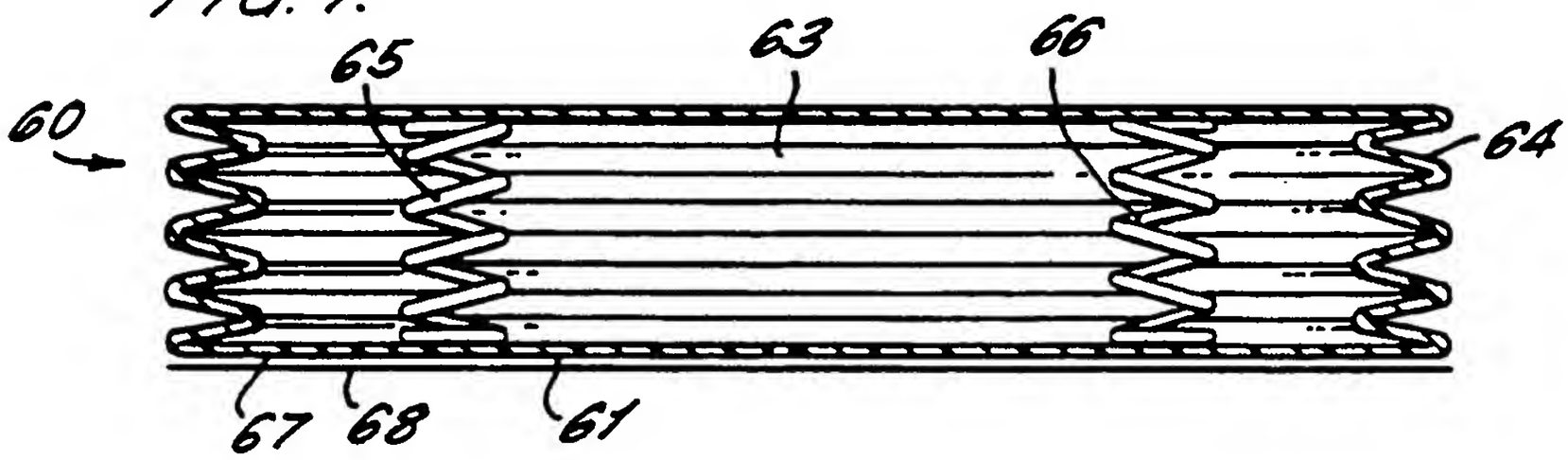


FIG. 8.

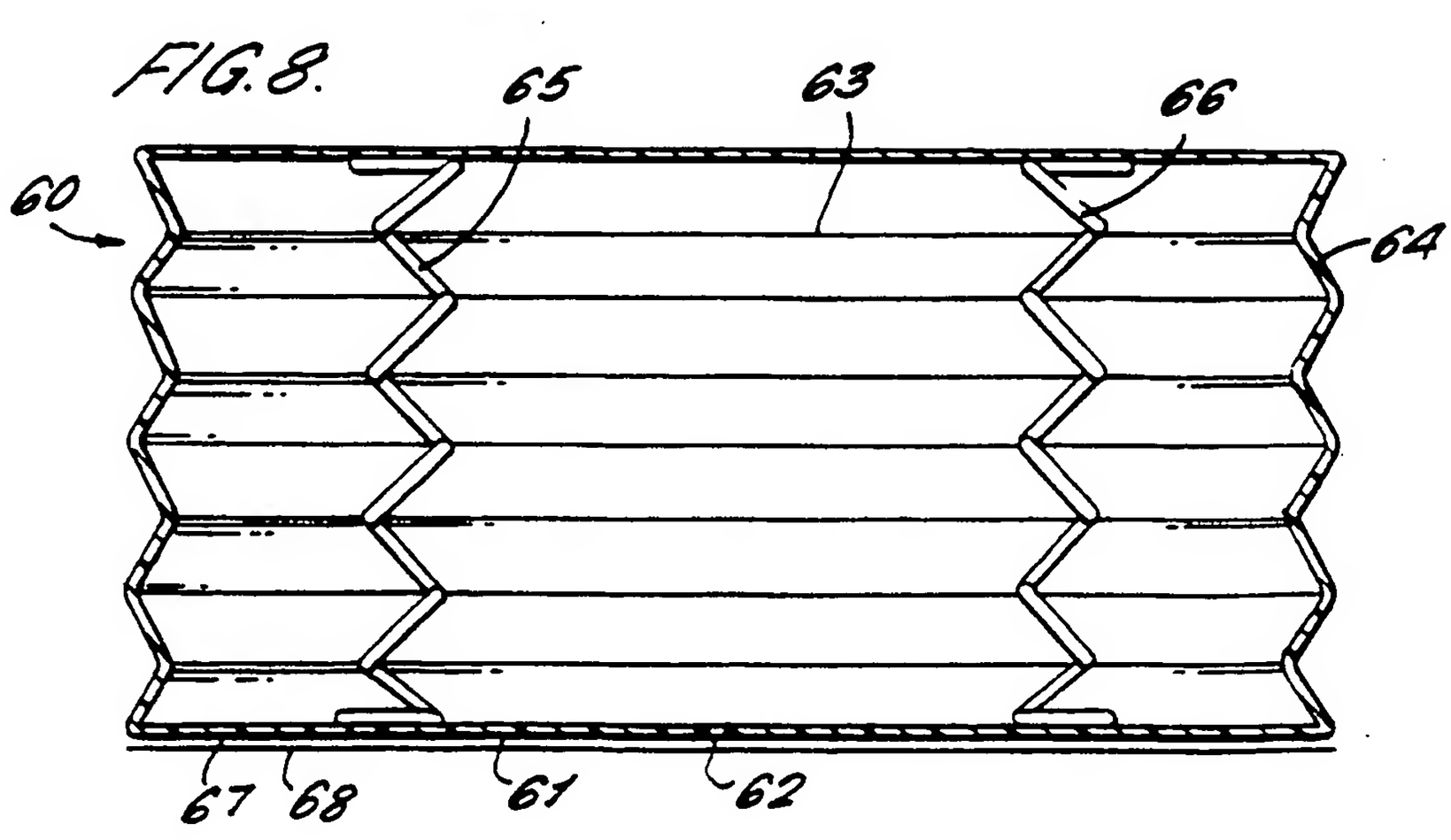


FIG. 9.

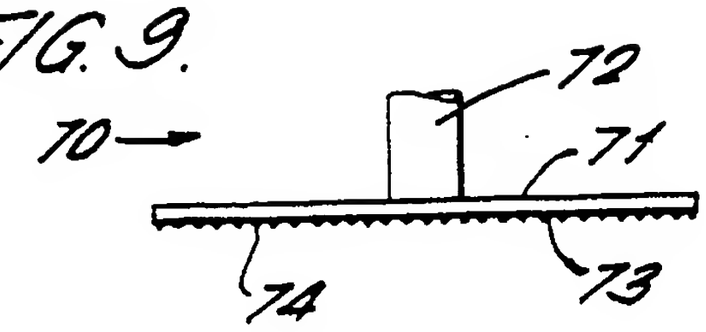


FIG. 10.

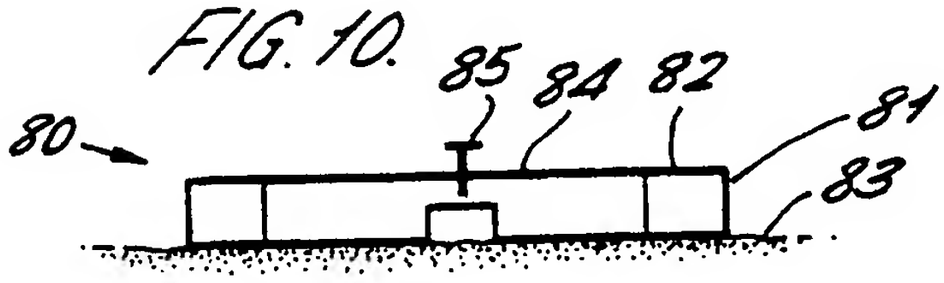


FIG. 11.

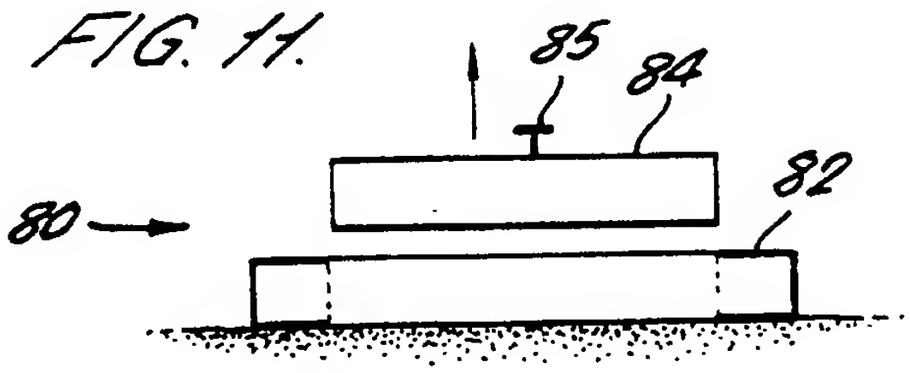


FIG. 12.

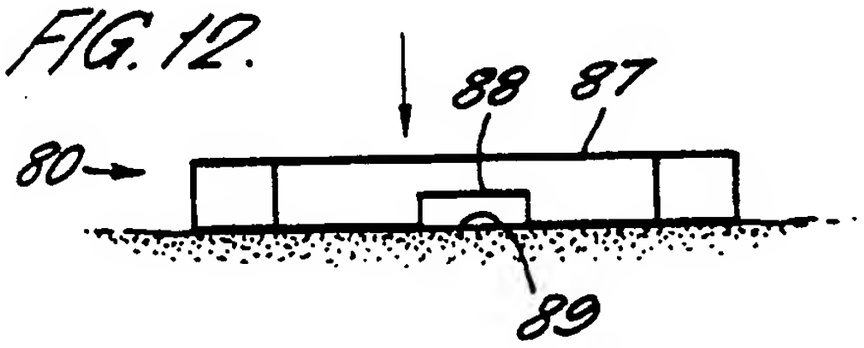


FIG. 13.

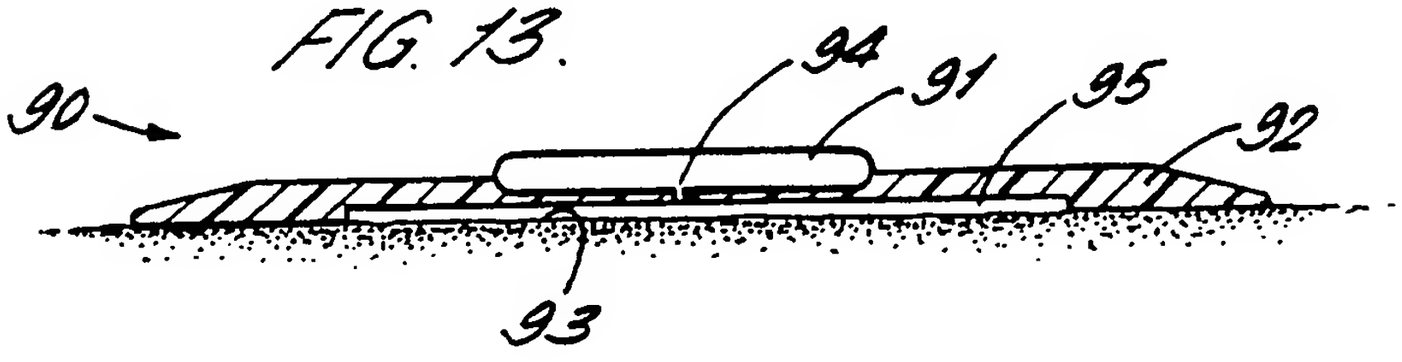


FIG. 14.

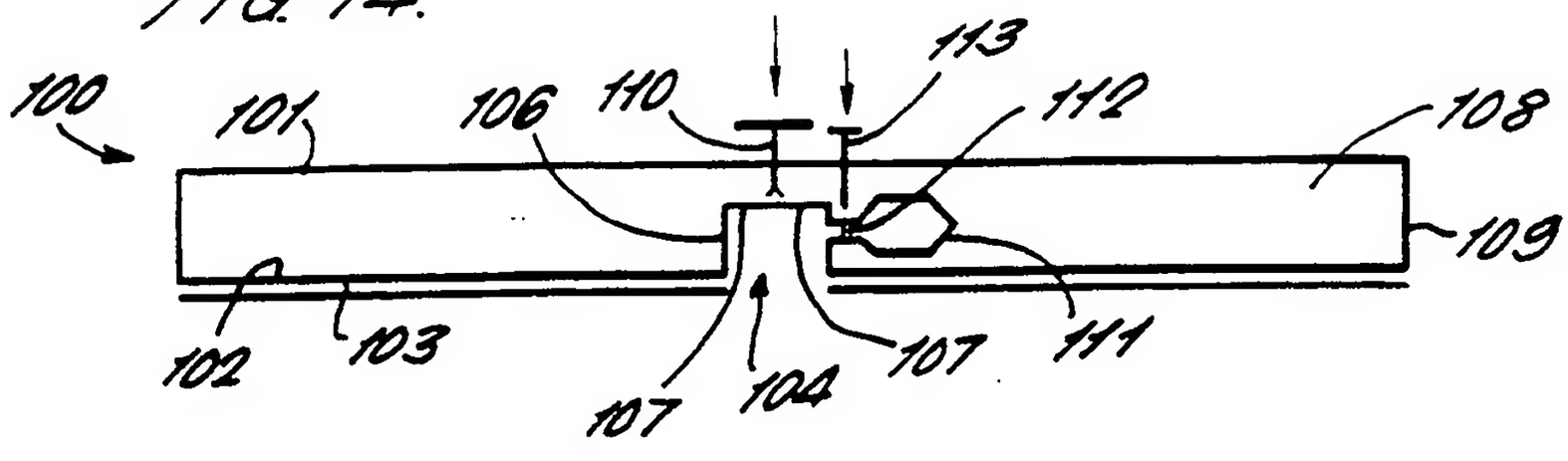


FIG. 15.

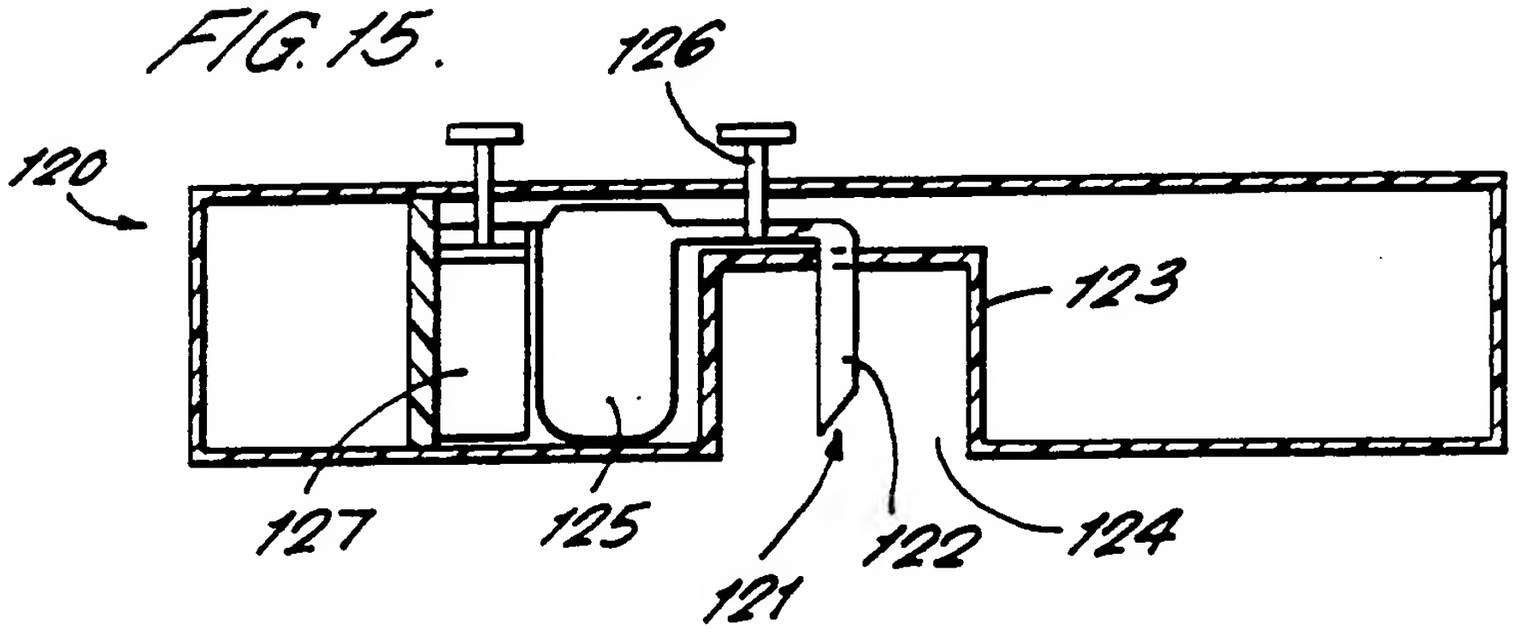


FIG. 16.

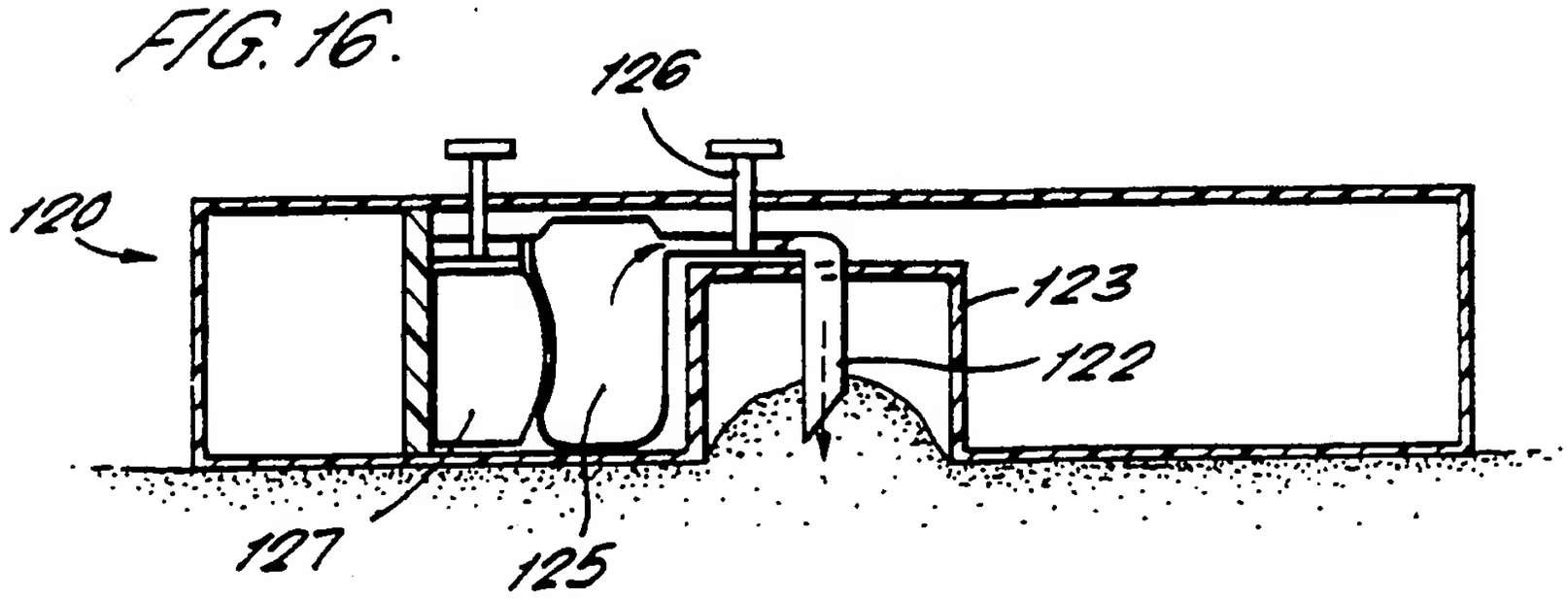


FIG. 17.

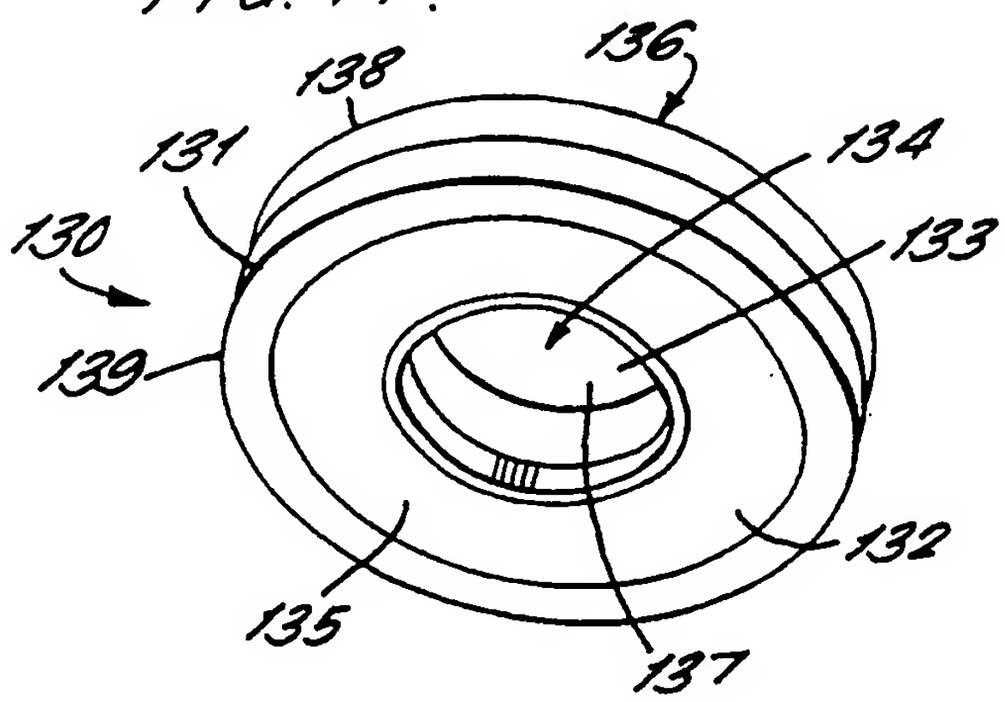


FIG. 18.

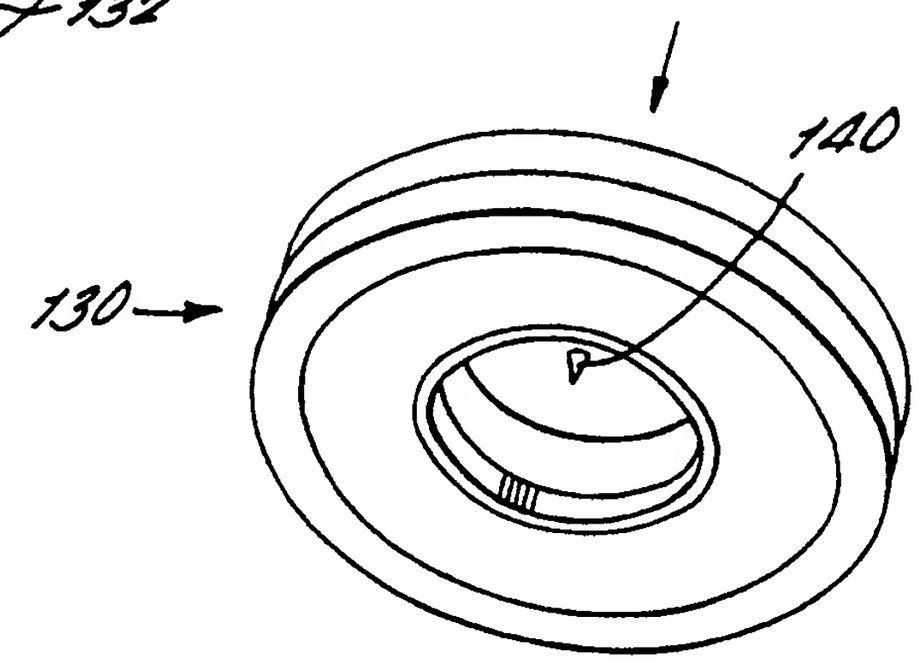


FIG. 19.

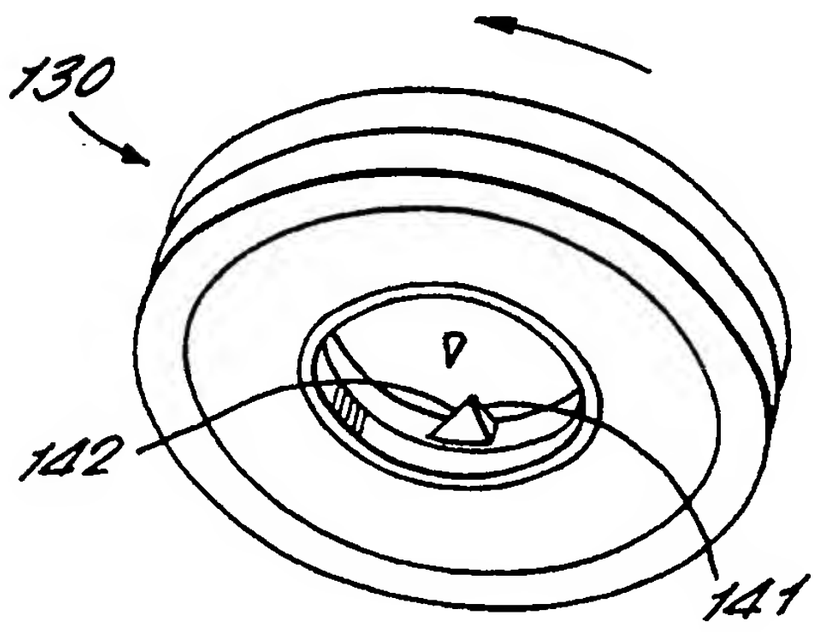
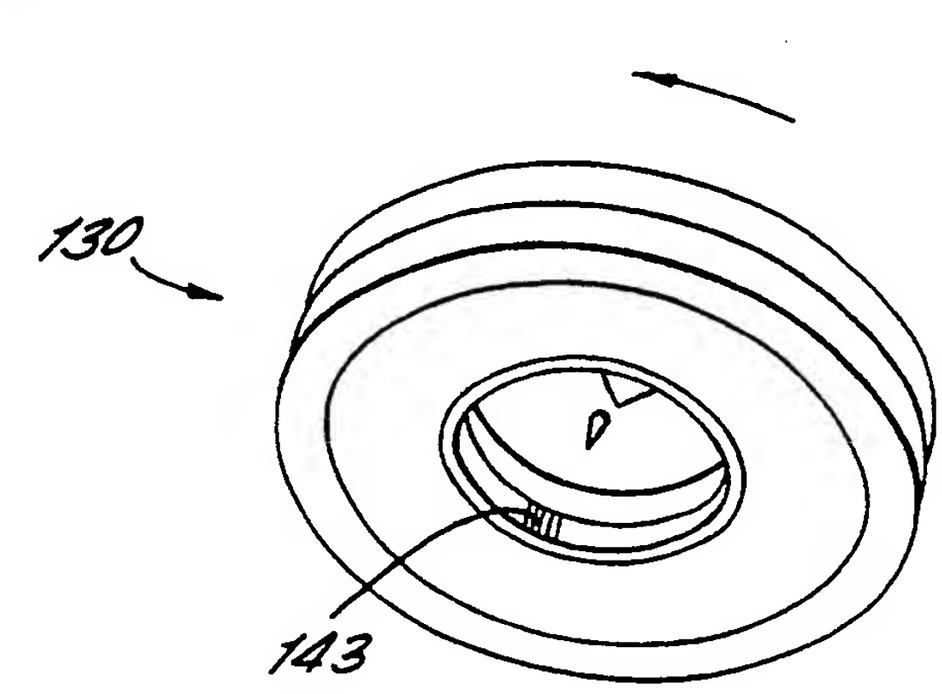


FIG. 20.



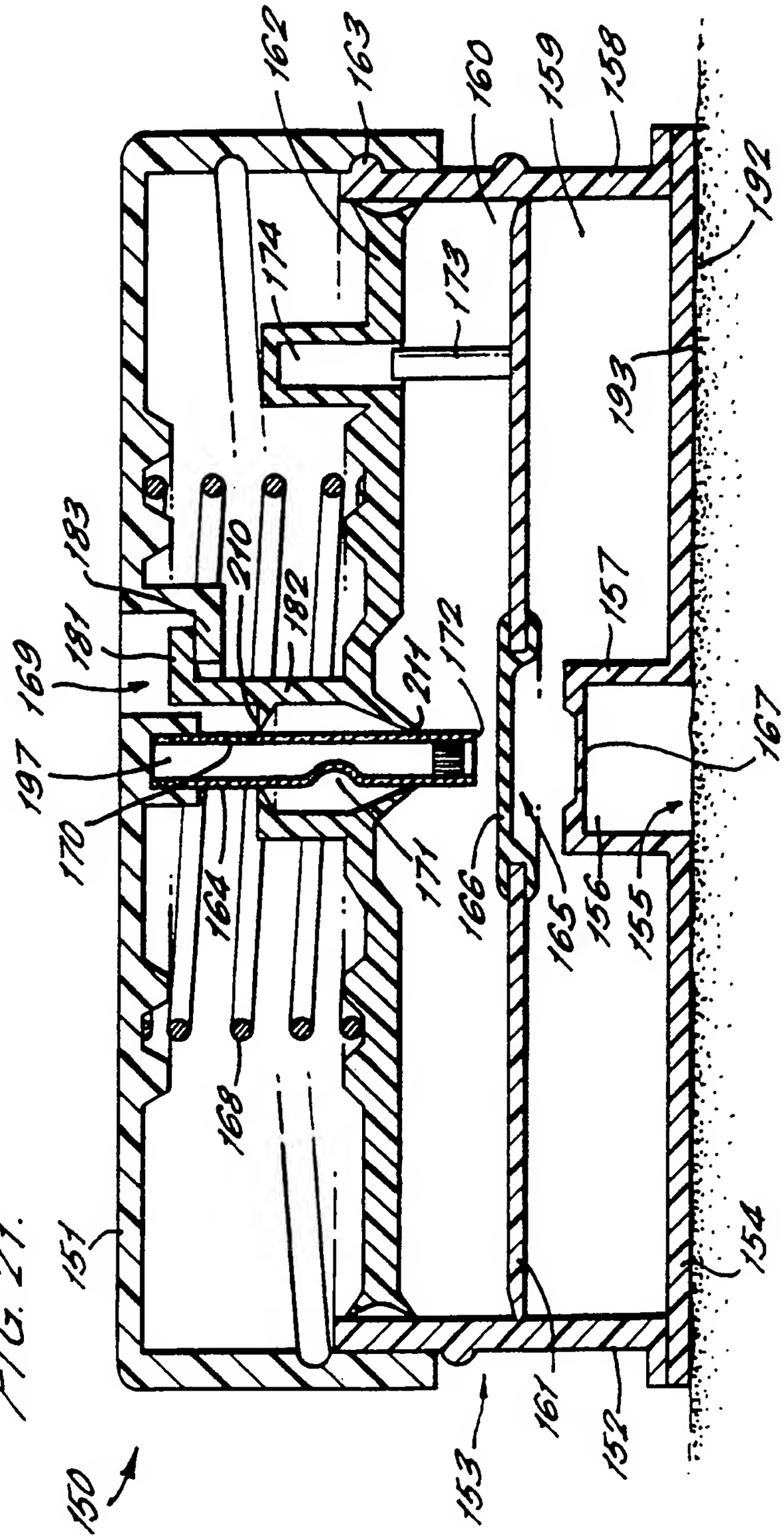

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FIG. 21.

FIG. 22.

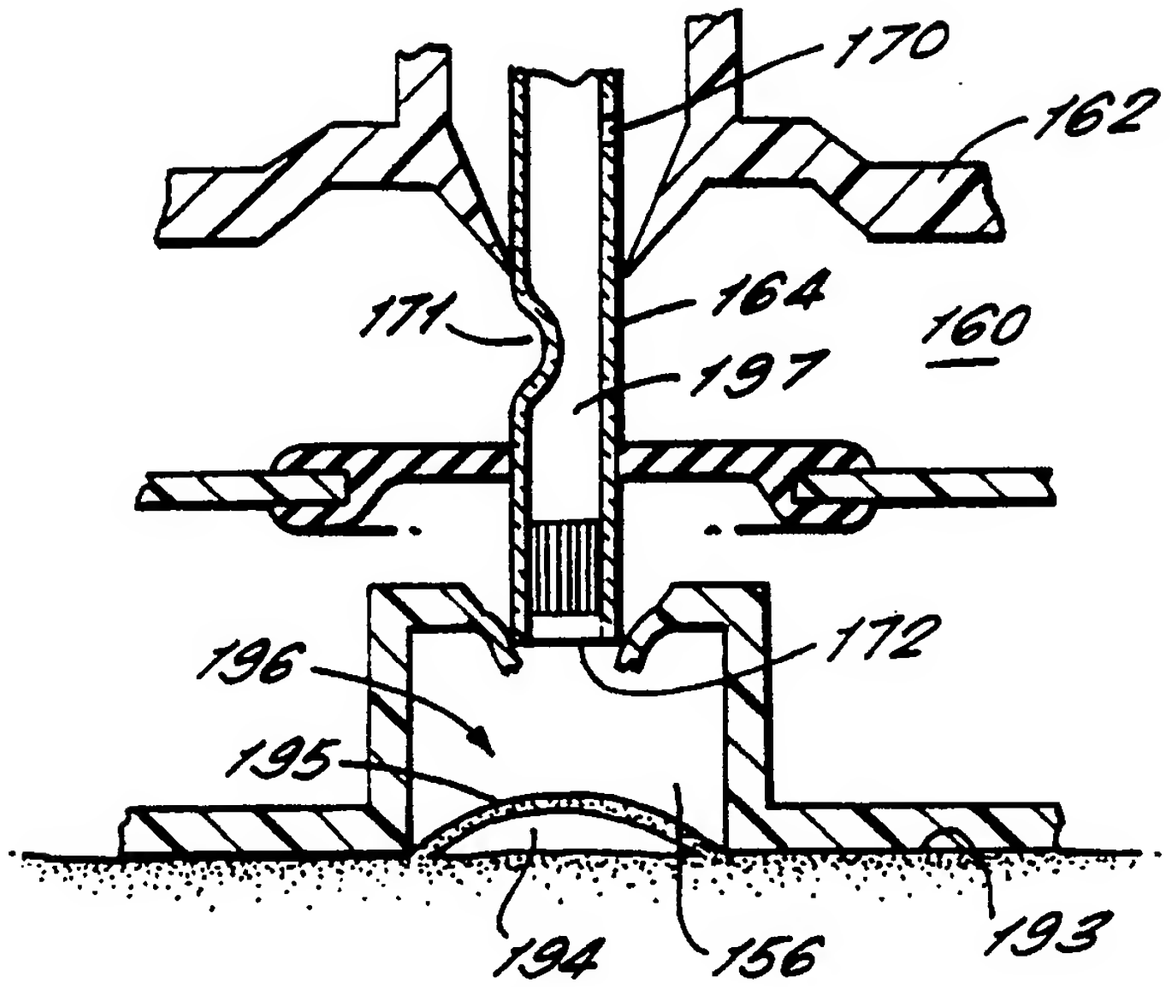


FIG. 23.

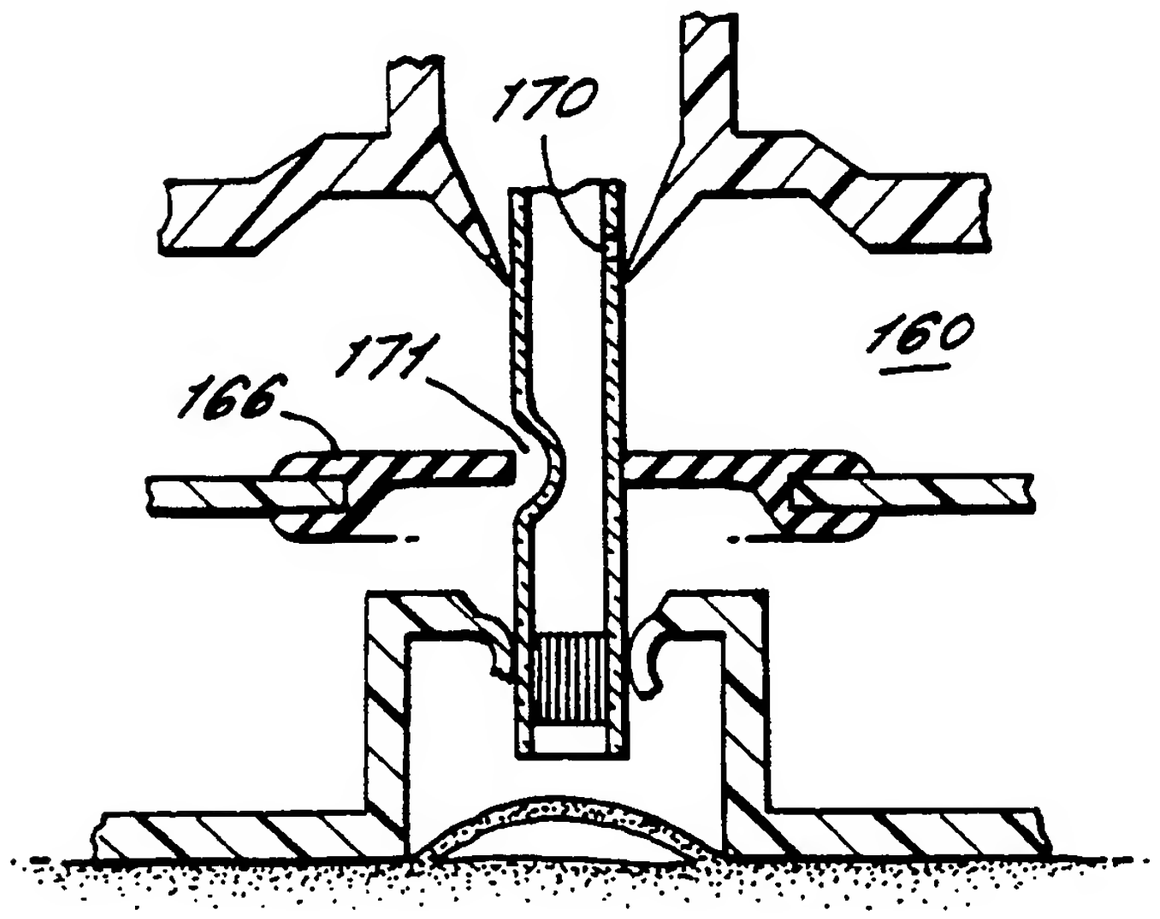


FIG. 24.

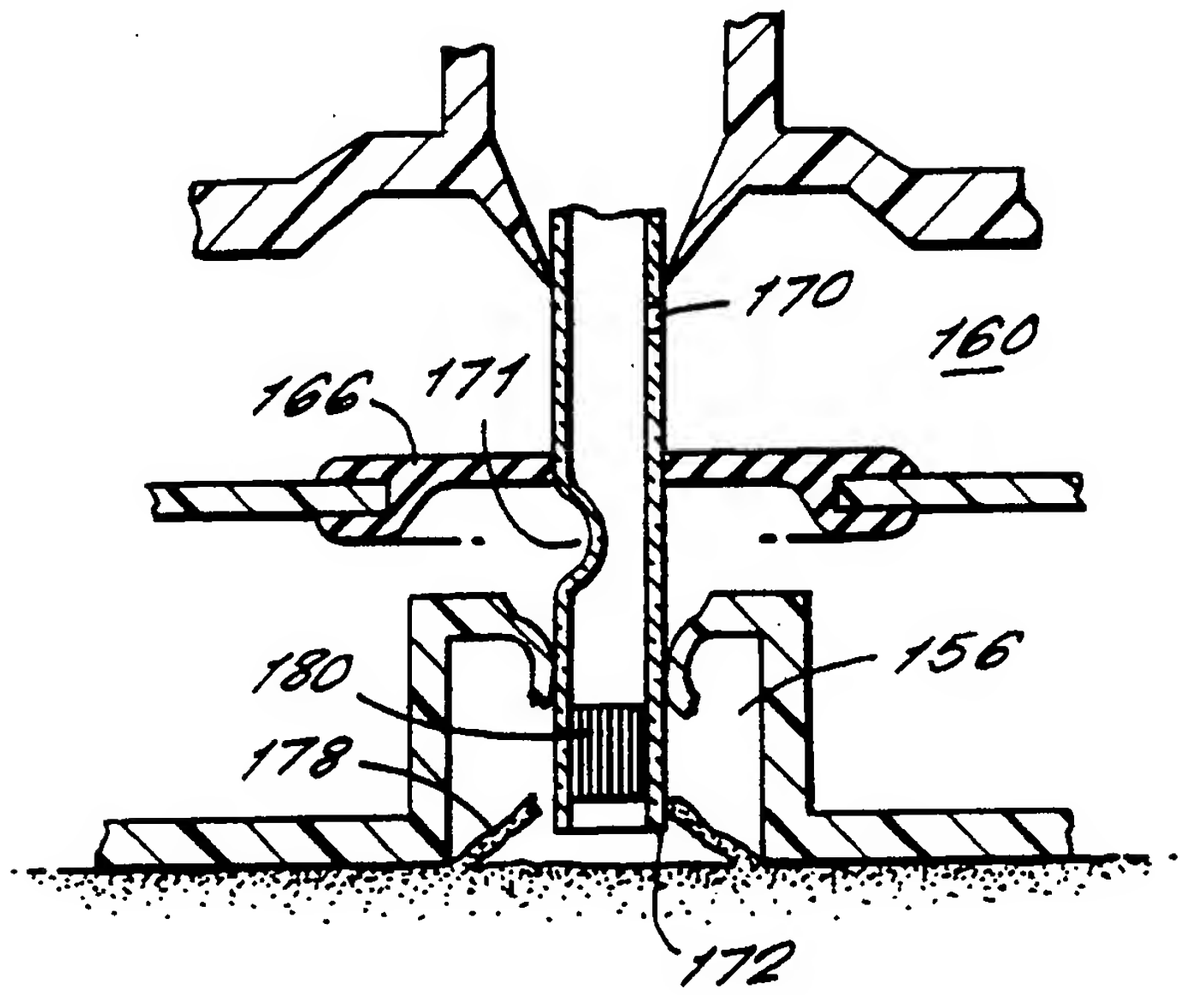


FIG. 27.

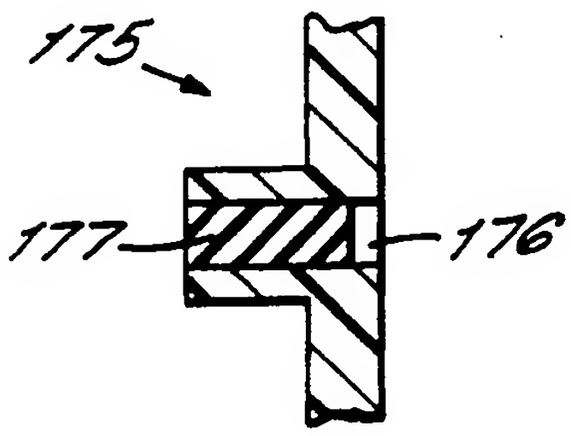


FIG. 28.

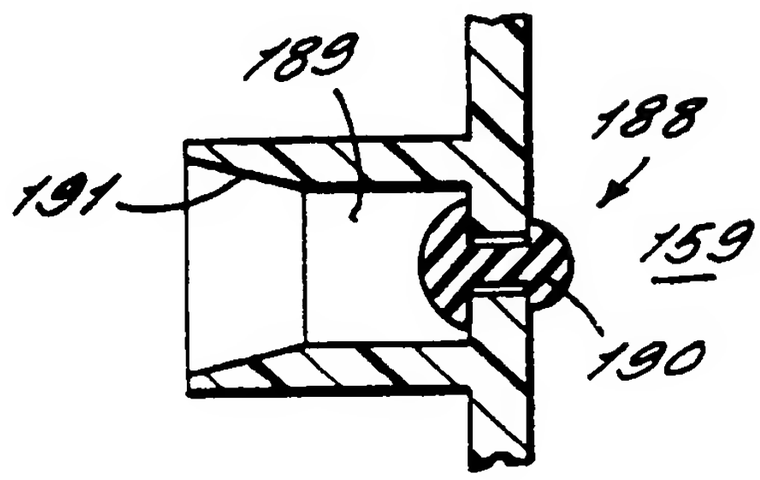


FIG. 29.

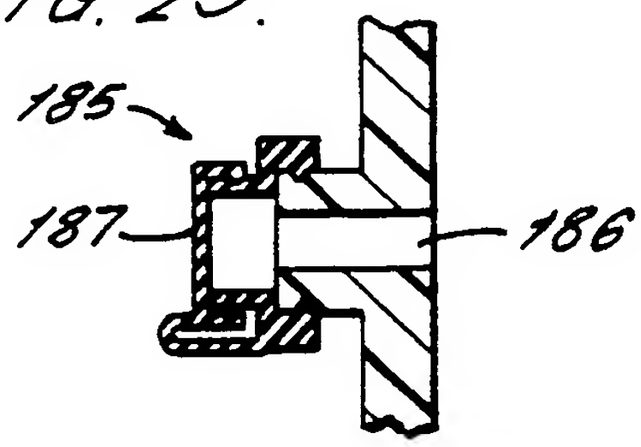


FIG. 25.

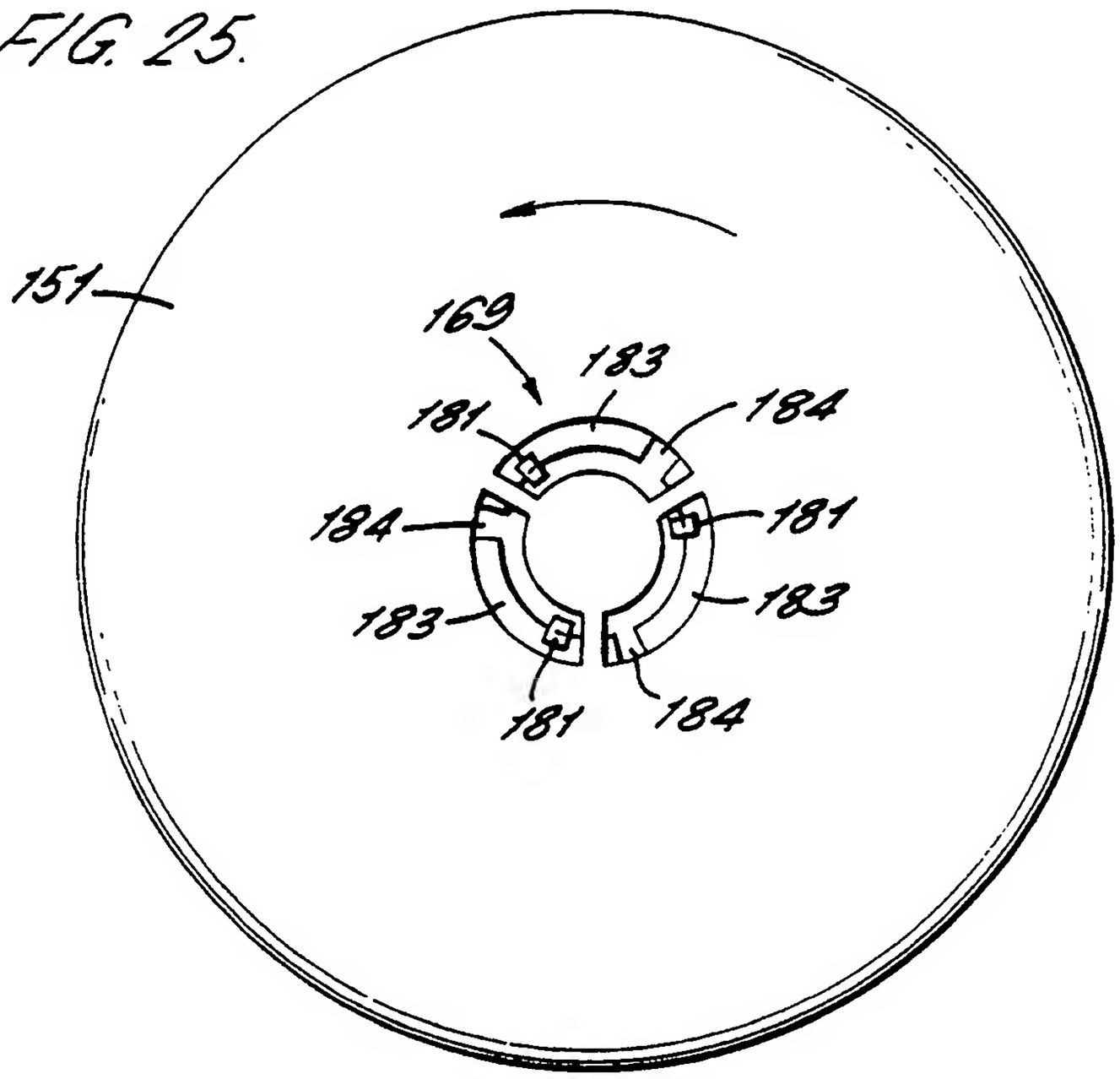


FIG. 26.

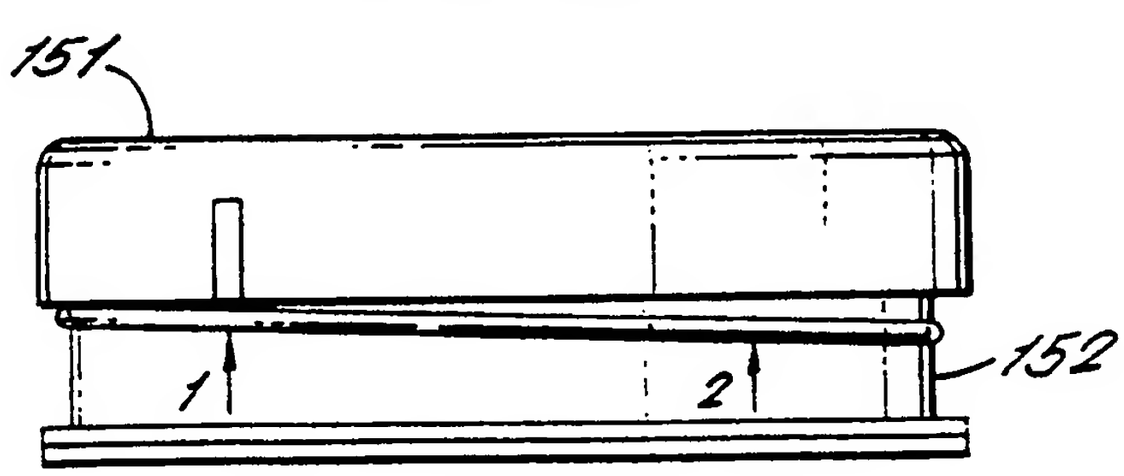


FIG. 30.

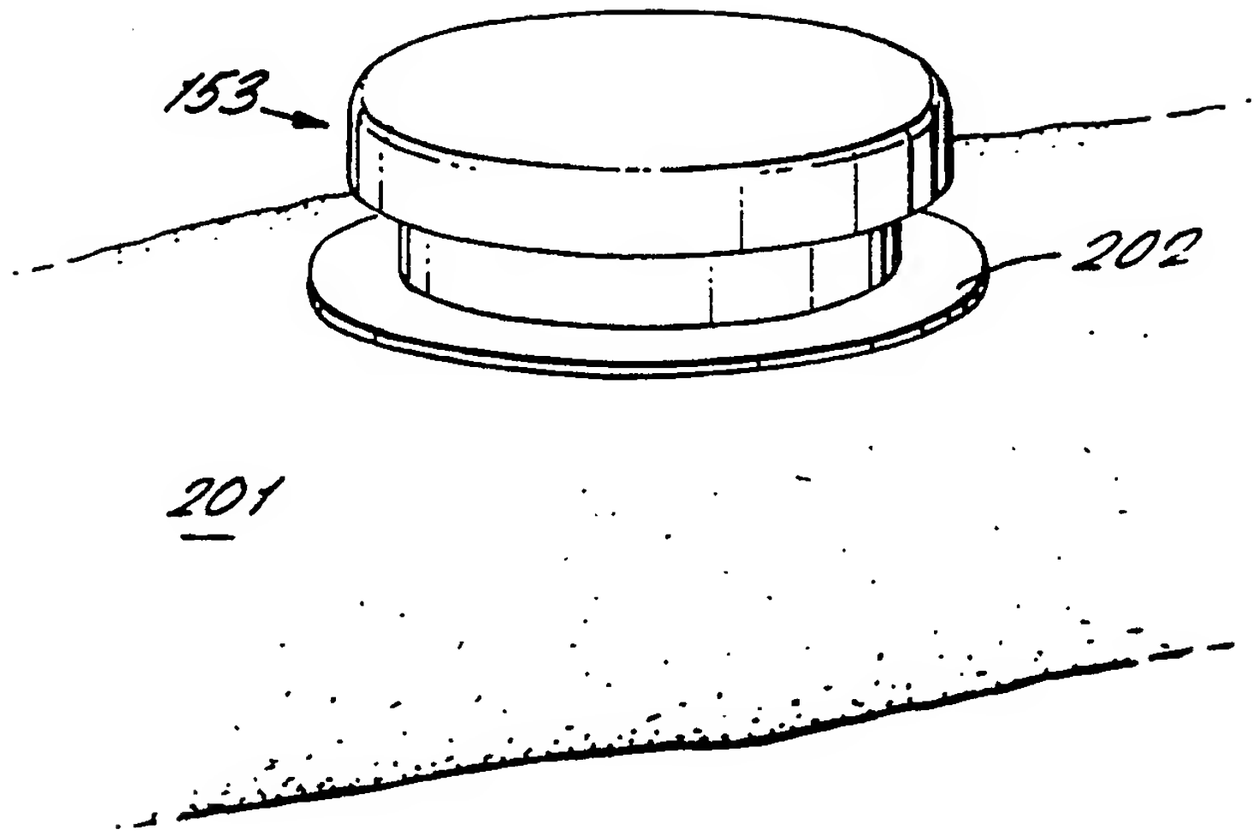


FIG. 31.

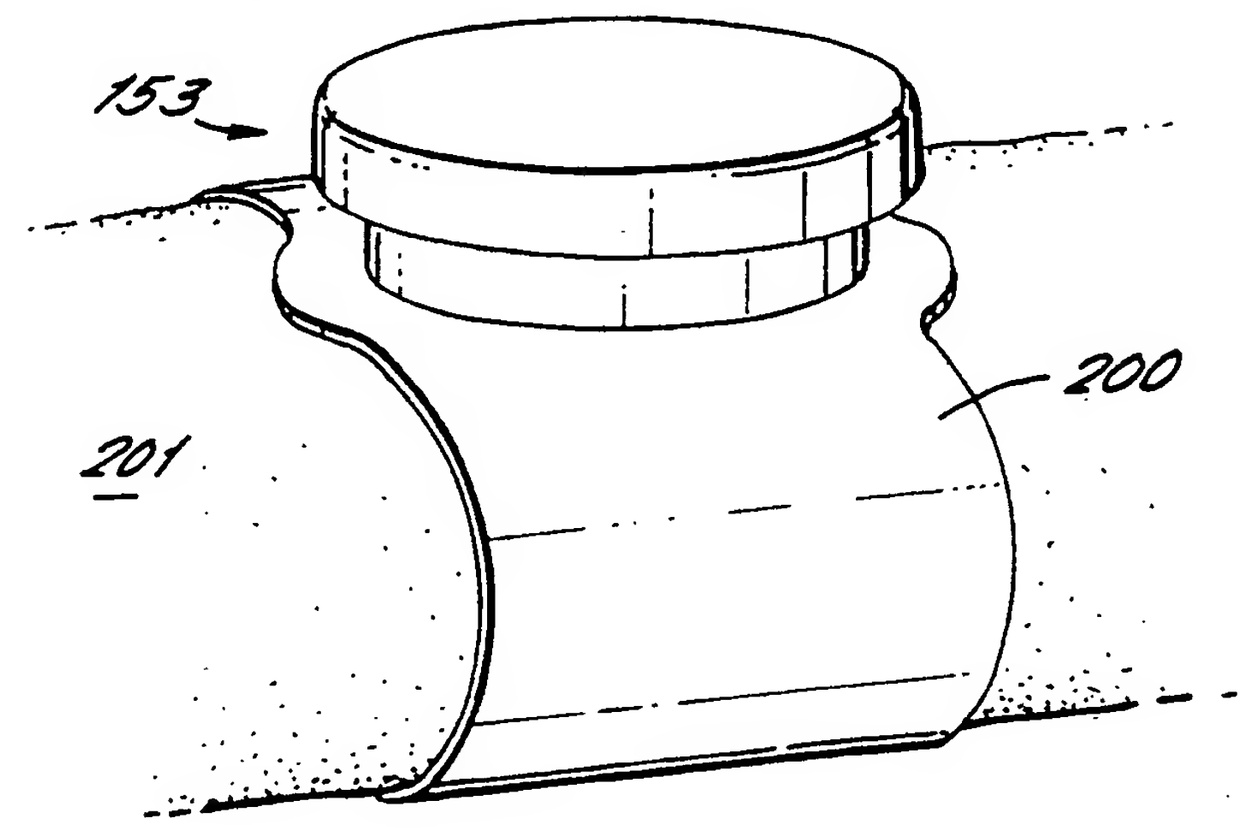


FIG. 32.

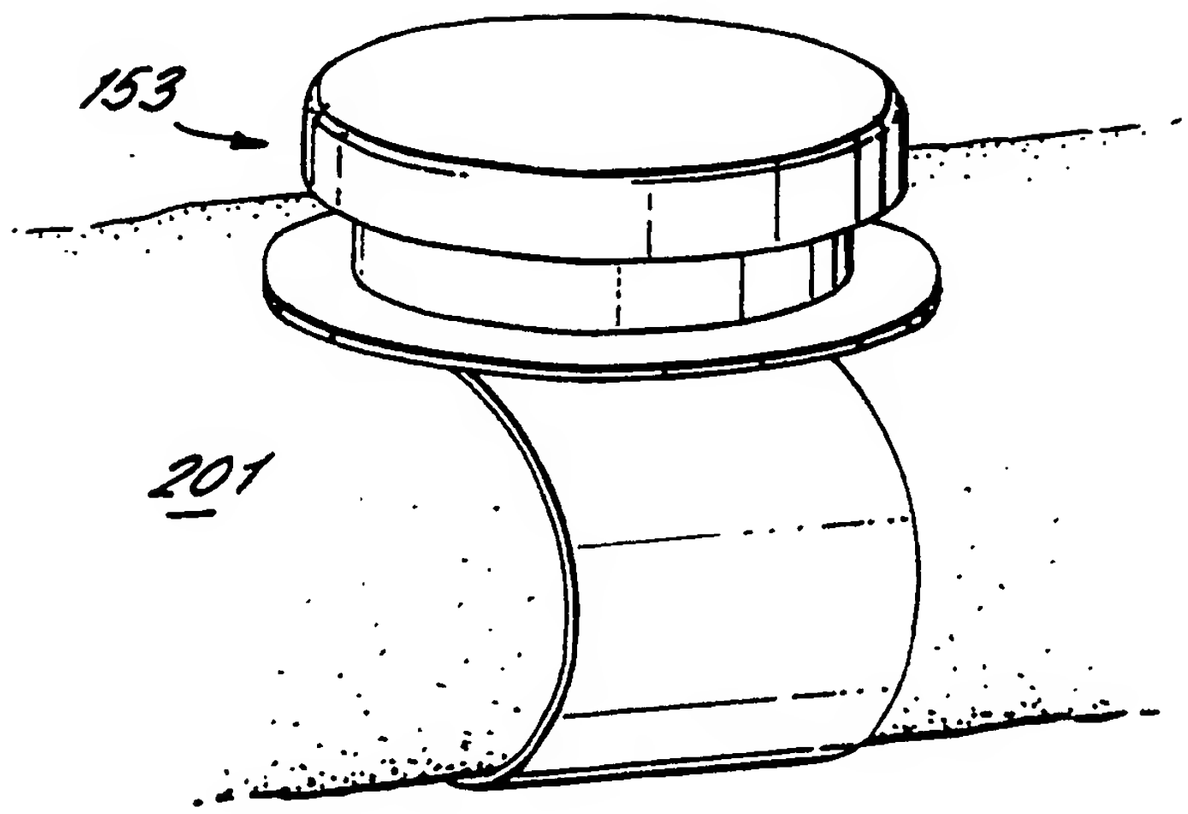
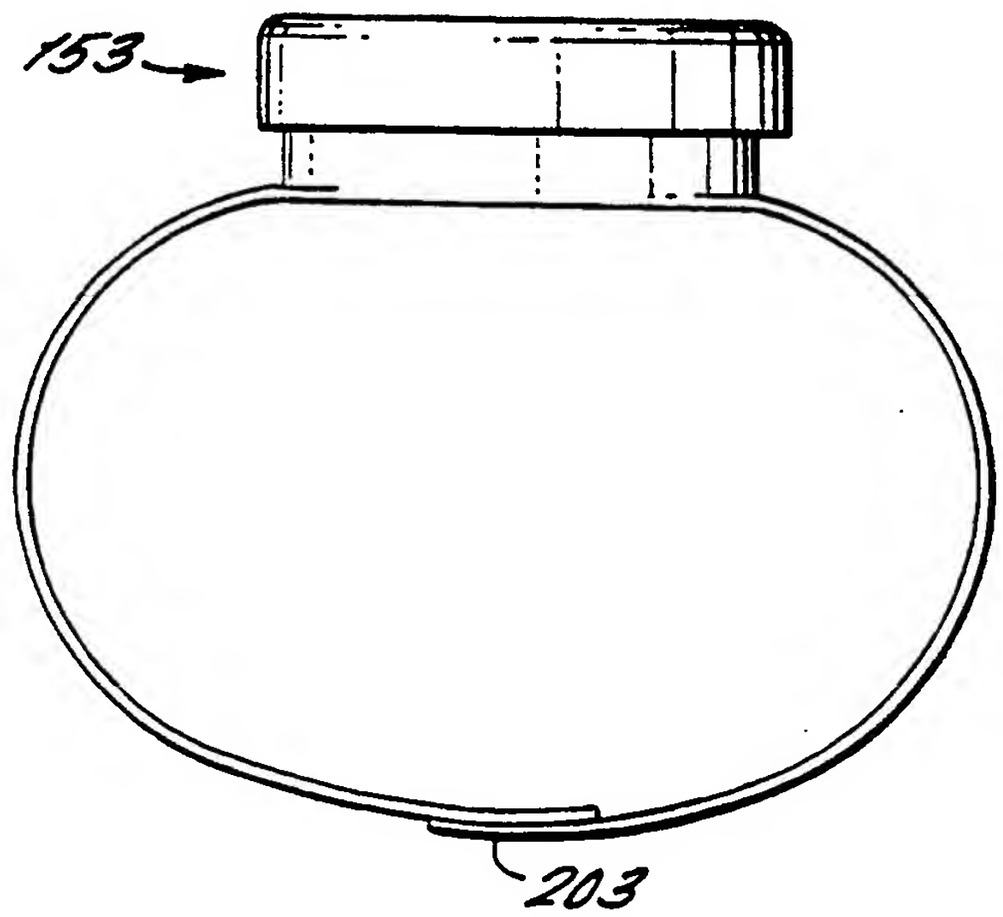


FIG. 33.



INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/00029

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 M 1/08 A 61 M 37/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 M

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,3486504 (L. AUSTIN) 30 December 1969, see column 2, line 58; claims 1-3; figures 1-3	1-3,5, 10,12, 14,18
A	DE,B,1238616 (AKTIEBOLAGET VACUUM-EXTRACTOR) 13 April 1967, see column 2, lines 26-34; figure 1	1-3,7, 16
A	FR,A,2303972 (SOCIETE DE RECHERCHES ET ETUDES TECHNIQUES) 8 October 1976, see page 2, lines 19-22; figures 1,2	6,15
A	FR,A, 983602 (LUNAUD) 14 February 1951, see column 2, line 13-22; figures 1,2	6,15

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08-05-1992	12.06.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 19-23 because they relate to subject matter not required to be searched by this Authority, namely:

Please see rule 39.1(iv) - PCT

Methods for treatment of the human or animal body by surgery or therapy,as well as diagnostic methods.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple Inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200029 SA 54684

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 09/06/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3486504	30-12-69	None	
DE-B- 1238616		None	
FR-A- 2303972	08-10-76	None	
FR-A- 983602		None	